VISIT…

The Chemistry of Radicals

CHAPTER 21

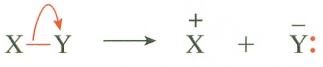
ALL OF THE MECHANISMS that have been presented so far have involved the reaction of electrophiles with nucleophiles. Carbocations and carbanions have been encountered as intermediates. In this chapter the chemistry of a new reactive intermediate, called a *radical* (or *free radical*), is presented. A **radical** is a species with an odd number of electrons. After a discussion of the structure of radicals, including their stability and geometry, various methods of generating them are described. Next, the general reactions that they undergo are presented. Finally, specific reactions involving radical intermediates are discussed.

MASTERING ORGANIC CHEMISTRY

- Understanding the Effect of the Structure of a Radical on Its Stability and the Rate and Regiochemistry of Its Reactions
- Predicting the Products of Radical Reactions
- Understanding the Mechanisms of Radical Reactions
- Using Radical Reactions in Synthesis

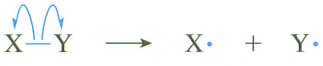
21.1 RADICALS

The reactions that we have encountered up to this point have involved the movement of pairs of electrons. For example, when a bond was broken, both electrons of that bond remained with one of the atoms. This process is termed **heterolytic bond cleavage:**



Heterolytic bond cleavage

Radicals are formed by **homolytic bond cleavage,** in which one electron of the bond remains with each of the atoms:



Homolytic bond cleavage

Note that an arrow with only half of an arrowhead is used to show the movement of a single electron that occurs in radical reactions, whereas the normal arrow shows the movement of a pair of electrons.

Important Convention

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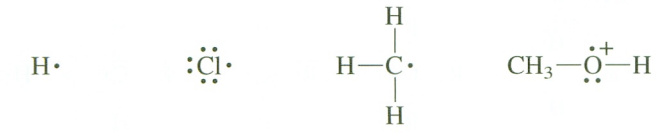
Some examples of radicals are the following:



Hydrogen atom	Chlorine atom	Methyl radical	Methanol radical cation

Hydrogen and chlorine atoms have an odd number of electrons and are radicals. The methyl radical is the simplest organic radical. It has one more electron than a carbocation and one fewer than a carbanion. The last example is a radical cation, which results from the loss of one electron from a normal molecule. Radical cations are important in mass spectrometry (see Chapter 15).

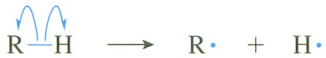
PROBLEM 21.1

Both nitrogen oxide (NO) and nitrogen dioxide (NO_2) are radicals. Show Lewis structures for these compounds.

21.2 Stability of Radicals

Because most radicals have an odd number of electrons on an atom, the octet rule cannot be satisfied at that atom. It is no surprise, then, that most radicals are unstable species and are quite reactive. They are most often encountered, like carbocations, as transient intermediates in reactions. However, alkyl radicals tend to have longer lifetimes than carbocations because they are less electron deficient, and therefore more stable. In fact, the lifetime of a radical can be appreciable in an environment where nothing is available with which to react. For example, hydrogen atoms are the principal type of matter in interstellar space. And the methyl radical has a lifetime of about 10 min when frozen in a methanol matrix at 77 K.

A comparison of the stabilities of different carbon radicals is provided by the bond dissociation energies of the bond between the carbon and a hydrogen. This is the energy that must be added when the reaction shown in the following equation occurs:



Bond dissociation energies for some carbon–hydrogen bonds are shown in Table 21.1.

The bond dissociation energy is the energy that must be supplied to generate a hydrogen atom and the carbon radical. Because a hydrogen radical is produced in each case, the difference between two bond dissociation energies reflects the difference in stability between the two carbon radicals. For example, because 104 − 98 = 6 kcal/mol (25 kJ/mol) less energy must be supplied to ethane than to methane to dissociate a hydrogen atom, the ethyl radical is 6 kcal/mol (25 kJ/mol) more stable than the methyl radical. Examination of Table 21.1 shows that the order of radical stabilities roughly parallels the order of carbocation stabilities presented in Section 8.7:

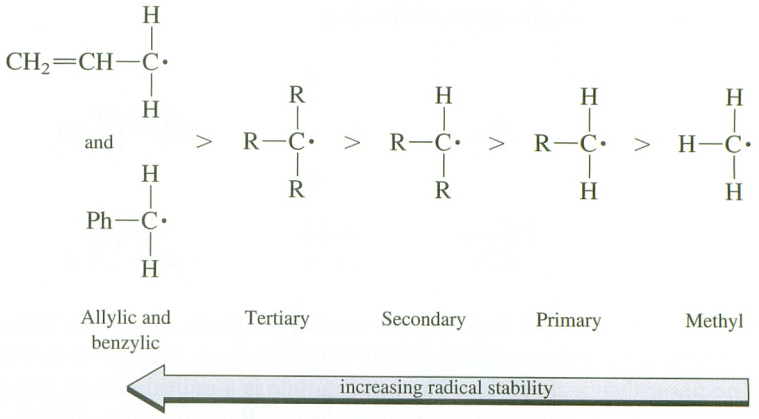
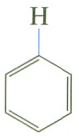
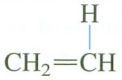
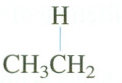
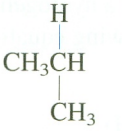
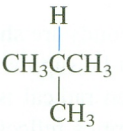
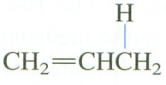
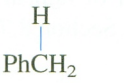


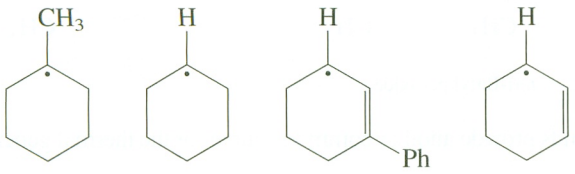
Table 21.1 Bond Dissociation Energies for Some Carbon–Hydrogen Bonds

Bond	Bond Dissociation Energies (kcal/mol [kJ/mol])
	110 (460)
	108 (452)
	104 (435)
	98 (410)
	95 (397)
	92 (385)
	89 (372)
	85 (356)

The reasons for this order of stabilities are the same for radicals as for carbocations. A primary radical is more stable than the methyl radical because overlap of a sigma MO on the adjacent carbon of the primary radical with the AO containing the odd electron provides a pathway for the electrons of the sigma bond to be delocalized onto the electron-deficient radical carbon, thus stabilizing it. (This is the same as the stabilization of carbocations by hyperconjugation described on page 273.) Secondary and tertiary radicals have additional stabilizing interactions of this type. Resonance stabilization is important in allylic and benzylic radicals. However, because they are more stable to begin with, the difference in stabilities between radicals is smaller than the difference in stabilities between the corresponding carbocations. In other words, the difference in stability between a secondary and tertiary radical is considerably smaller than that between a secondary and tertiary carbocation. This is one reason why radicals are not as prone to rearrangements as carbocations are.

PROBLEM 21.2

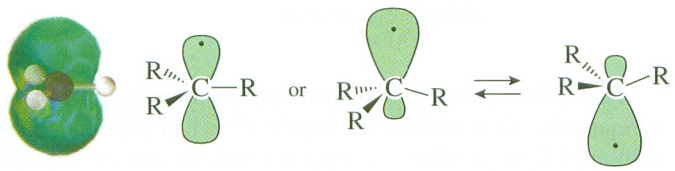
Arrange these radicals in order of increasing stability:



21.3 GEOMETRY OF CARBON RADICALS

If an attempt were made to apply the rules of valence shell electron pair repulsion theory to radicals, it would not be clear how to treat the single electron. Obviously, a single electron should not be as "large" as a pair of electrons, but it is expected to result in some repulsion. Therefore, it is difficult to predict whether a radical carbon should be sp^2 hybridized with trigonal planar geometry (with the odd electron in a p orbital), sp^3 hybridized with tetrahedral geometry (with the odd electron in an sp^3 AO), or somewhere in between. Experimental evidence is also somewhat uncertain. Studies of the geometry of simple alkyl radicals indicate that either they are planar or, if they are pyramidal, inversion is very rapid.

This model shows the electron density for the odd electron of the planar methyl radical. The radical electron is in a p orbital perpendicular to the plane of the atoms.



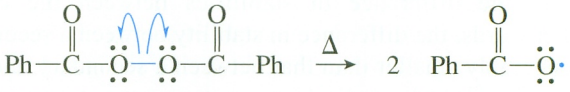
A trigonal planar radical

A rapidly inverting pyramidal radical

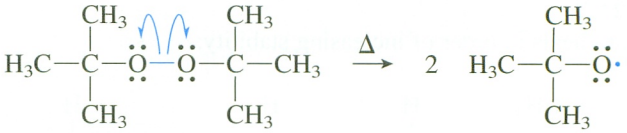
The important consequence of this is that reactions that involve radicals, like reactions that involve carbocations, result in the loss of stereochemistry (racemization) at the radical carbon.

21.4 GENERATION OF RADICALS

When a compound that has an especially weak bond is heated, the weak bond is selectively cleaved to produce radicals. Because the bond energy of the oxygen–oxygen bond is small, only about 30 kcal/mol (126 kJ/mol), peroxides readily undergo bond homolysis when they are heated to relatively low temperatures (80°–100°C). Commercially available peroxides, such as benzoyl peroxide and *tert*-butyl peroxide, are commonly used as sources of radicals.



Benzoyl peroxide

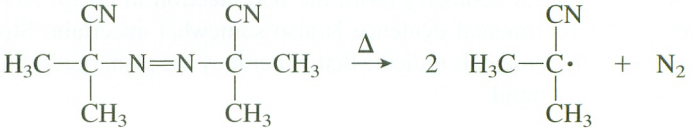


tert-Butyl peroxide

Azo compounds provide another common source for the thermal generation of radicals.

An azo compound

In this case it is not that the carbon–nitrogen bond is so weak; rather, it is the formation of the strong nitrogen–nitrogen triple bond of the N_2 product that enables the reaction to occur at relatively low temperatures. Azobis(isobutyronitrile), also known as AIBN, has been widely used as a radical source because it is commercially available. In addition, it undergoes bond homolysis at lower temperatures than other azo compounds (below 100°C) because the product radicals are tertiary and are stabilized by resonance.

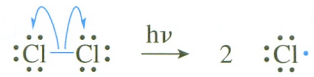


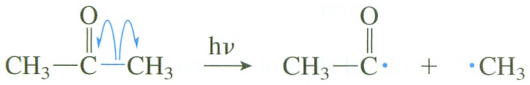
Azobis(isobutyronitrile)
AIBN

Radicals can also be generated by the action of ultraviolet or visible light on certain compounds. As described in Chapter 15, when a compound is excited by absorbing a photon of light, an electron is promoted to an unoccupied orbital. Because this orbital is usually antibonding in character, some bond in the excited molecule is weakened and may cleave in a homolytic fashion. For this reason, many photochemical reactions involve radicals. Examples of photochemically induced homolytic bond cleavages are

provided in the following equations. *(Recall that hν is used to indicate the action of light on a compound.)*

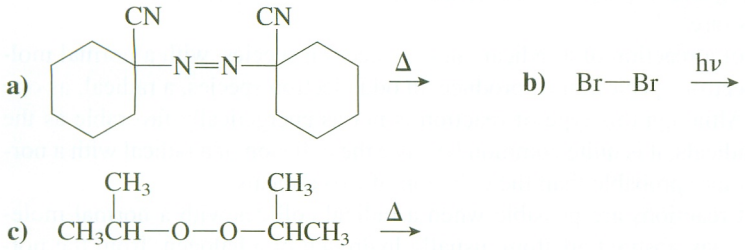
Important Convention





PROBLEM 21.3

Show the radicals produced in these reactions:



21.5 General Radical Reactions

A radical is unstable because of its odd electron. To form a stable molecule, the radical needs to use that odd electron to form a bond to another atom. The reaction of two radicals, each with an odd number of electrons, allows the formation of a molecule (or molecules) that is stable because it has an even number of electrons and has the octet rule satisfied for all of its atoms.

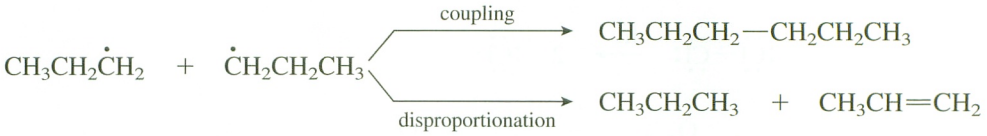
A common way for two radicals to form a stable product is by **coupling** to form a bond between their radical centers.

Coupling

Another way that radicals can react to form stable products is for one radical to abstract a hydrogen atom from the carbon adjacent to the radical center of another radical in a process called **disproportionation.** This results in the formation of a pi bond in one of the radicals:

Disproportionation

Many radicals can react by both of these pathways, as illustrated in the following equation showing the coupling and disproportionation of propyl radicals:

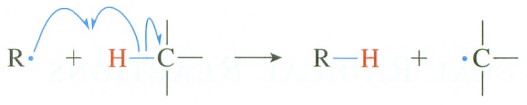


As might be expected, the ratio of disproportionation to coupling increases with increasing steric hindrance at the radical centers.

Coupling and disproportionation are energetically very favorable and tend to occur nearly every time two radicals collide. These reactions would dominate radical chemistry but for the fact that the concentration of radicals is usually very small. Therefore, the rate of coupling and disproportionation reactions is often slow because the collision of two radicals is rare.

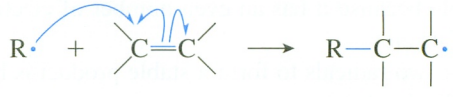
The product of a reaction of a radical, an odd electron species, with a normal molecule, an even electron species, must produce an odd electron species, a radical, as one of the products. Although this type of reaction is not as energetically favorable as the reaction of two radicals, it is quite common because the collision of a radical with a normal molecule is more probable than the collision of two radicals.

Two different reactions are possible when a radical collides with a normal molecule. The radical may abstract an atom, usually hydrogen or a halogen, from the normal molecule:



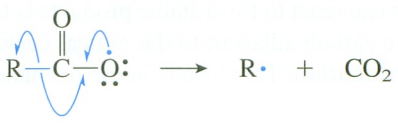
Abstraction

If the normal molecule has a double bond, the radical can add to the pi bond:



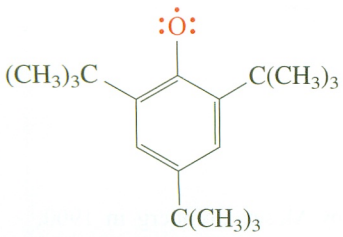
Addition

Finally, radicals can fragment to a smaller radical and a normal molecule in a process that is the reverse of addition. As an example, radicals derived from carboxylic acids eliminate carbon dioxide very rapidly.

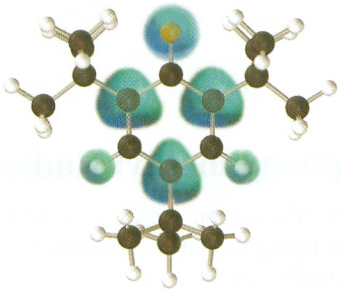


Fragmentation

The rates of all of these radical reactions are affected by the same factors that affect the rates of other reactions. More stable radicals are formed more readily, react more slowly, and have longer lifetimes. In addition, steric hindrance can prevent two radicals from approaching close enough to couple, thus increasing the lifetime of the radical. As an example of the importance of steric factors, the 2,4,6-tri-*tert*-butylphenoxy radical does not couple in solution and can actually be isolated as a solid.



2,4,6-tri-*tert*-Butylphenoxy radical



The green areas in this model show the locations of the odd electron density in the radical, primarily on the oxygen and the positions ortho and para to it. (This is consistent with the location of the odd electron in the resonance structures that can be written for this radical.) Note how the positions with odd electron density are shielded by the bulky *tert*-butyl groups.

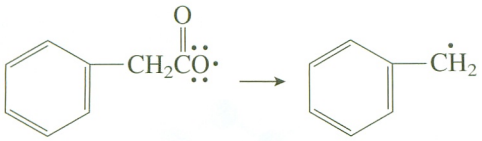
PROBLEM 21.4

Explain which of these reactions would be faster:

a) $:\dot{\underset{\cdot\cdot}{\underset{\cdot\cdot}{Br}}}\cdot + CH_3CH_2CH_3 \longrightarrow HBr + CH_3\dot{C}HCH_3$

or

$:\dot{\underset{\cdot\cdot}{\underset{\cdot\cdot}{Br}}}\cdot + CH_3CH(CH_3) \longrightarrow HBr + CH_3\dot{C}(CH_3)_2$

b) 

or

PROBLEM 21.5

Suggest structures for products that might be formed in these reactions:

a) $:\dot{\underset{\cdot\cdot}{\underset{\cdot\cdot}{Br}}}\cdot + CH_3CH{=}CH_2 \longrightarrow$

b) $CH_3COOCCH_3 \xrightarrow{\Delta}$

c) $2\ CH_3CH_2CH_2\dot{C}H_2 \longrightarrow$

d) $2\ NO_2 \rightleftharpoons$

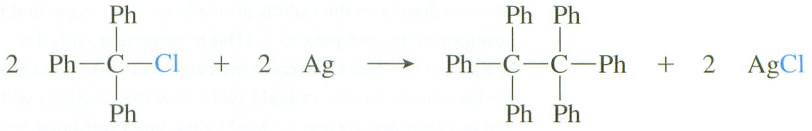
e) $CH_3C(CH_3)_2{-}N{=}N{-}C(CH_3)_2CH_3 \xrightarrow{\Delta}$

Now let's examine some actual radical reactions that result from combinations of these general reactions.

Focus On

The Triphenylmethyl Radical

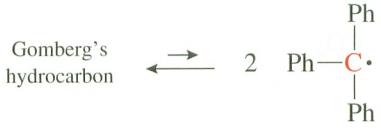
The existence of a carbon radical was first proposed by Moses Gomberg in 1900. Gomberg was trying to prepare hexaphenylethane from triphenylmethyl chloride according to the following equation:

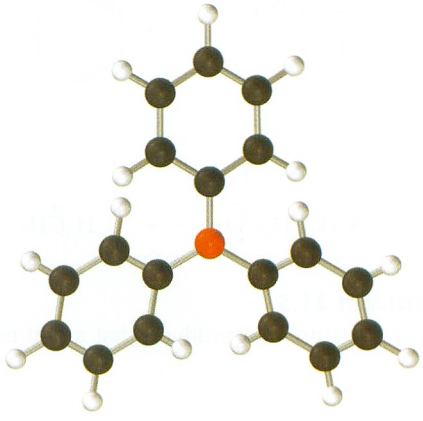


Triphenylmethyl chloride Hexaphenylethane

He obtained a colorless hydrocarbon, which he thought was hexaphenylethane. However, this compound is highly reactive, much more so than would be expected for hexaphenylethane. Furthermore, when this compound is dissolved in solvents such as benzene, it gives a yellow solution. The intensity of the yellow color increases as the solution is heated, indicating that the concentration of the colored species increases as the temperature increases. Furthermore, the color is discharged when oxygen is bubbled through the solution.

Gomberg correctly hypothesized that the hydrocarbon is in equilibrium with triphenylmethyl radicals:

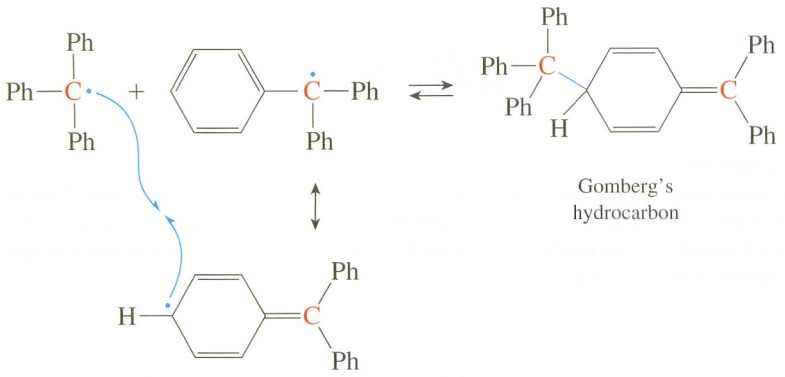




The equilibrium constant has been determined to be 2×10^{-4} M, which means that about 1% of a 1 *M* solution of the hydrocarbon is dissociated into radicals. These radicals react with any oxygen in the solution to give colorless products.

Today, we recognize that the ability of triphenylmethyl radicals to exist free in solution is due to two factors. First, the radical has considerable resonance stabilization. Second, and more important, there is considerable steric hindrance to the dimerization of the radical due to the three bulky phenyl groups. In fact, it has recently been shown that Gomberg's hydrocarbon is not hexaphenylethane but actually results from one

triphenylmethyl radical bonding to the para position of a phenyl group on the second, even though this results in the loss of the aromatic resonance energy of one ring:

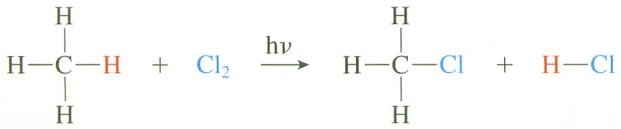


Gomberg's hydrocarbon

Gomberg's proposal was the first suggestion that carbon is not always tetravalent. The acceptance of the triphenylmethyl radical by the scientific community helped facilitate the development of mechanistic organic chemistry with its trivalent carbocations, carbanions, and radicals.

21.6 HALOGENATION

The reaction of methane with chlorine to form chloromethane is induced by light:



This substitution reaction follows a radical chain mechanism, as outlined in Figure 21.1. Radical chain mechanisms involve three types of steps:

Initiation step: In this step, a normal compound undergoes homolytic bond cleavage to generate radicals.

Propagation steps: A radical chain reaction often has several propagation steps. In each of these steps, a radical reacts with a normal compound to produce a new radical. The final propagation step of a chain reaction produces the same radical that reacts in the initial propagation step, so the process can begin anew.

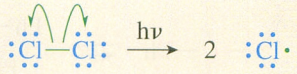
Termination steps: In termination steps, two radicals react to give nonradical products by coupling or disproportionation. These steps destroy radicals.

The radicals produced by one initiation step cause a very large number of propagation steps to occur before they are finally destroyed by a termination step. Termination steps are slower than propagation steps because the concentration of radicals is small. Therefore, the probability of one radical encountering another so that a termination can occur is low.

As shown in Figure 21.1, the initiation step in the chlorination of methane is light-induced cleavage of Cl_2 to produce two chlorine atoms. A chlorine atom then abstracts a hydrogen from methane to produce a methyl radical. The methyl radical abstracts a chlorine

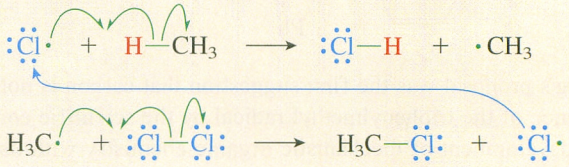
Initiation

The weak chlorine–chlorine bond is broken by light.



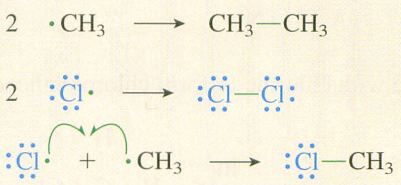
Propagation

A chlorine atom abstracts a hydrogen atom from methane in the first propagation step. Then the methyl radical that is formed abstracts a chlorine atom from Cl_2. The chlorine atom that is produced in the second propagation step reacts again as in the first propagation step. This cycle of two propagation steps is repeated many times in a chain reaction.



Termination

The termination steps include all of the possible radical coupling reactions.



Active Figure 21.1 ORGANIC Chemistry Now™

RADICAL CHAIN MECHANISM OF THE CHLORINATION OF METHANE. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

atom from Cl_2 to produce a molecule of the product, chloromethane, and another chlorine atom. This chlorine atom abstracts a hydrogen from another methane molecule, and the cycle is repeated. A single initiation step causes a very large number (as many as 1000 or more) of propagation cycles to occur. The large number of propagation cycles is characteristic of a chain reaction. Eventually, one of the radicals encounters another radical, and a termination reaction occurs. It is important to recognize that a chain reaction follows the pattern

one initiation reaction,
many propagation cycles,
one termination reaction.

Although the initiation and termination steps are important in the mechanism of a chain reaction, almost all of the products are formed as the result of the propagation steps because there are so many more of them. An equation for the overall reaction can be obtained by summing the propagation steps and canceling species that appear on both sides of the equation:

$$\cdot\!\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}\!\cdot + CH_4 \longrightarrow HCl + \cdot CH_3$$

$$\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + \cdot\!\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}\!\cdot$$

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

The amount of chloromethane that is produced by the termination steps is negligible in comparison to the amount produced by the propagation steps. Likewise, the amount of ethane produced by termination steps is so small that it is hard to detect and can be neglected in the balanced equation for the reaction (but not in the mechanism).

Radical chlorination is a difficult reaction to control. As the reaction proceeds and the initial product, chloromethane, accumulates, it can also undergo hydrogen abstraction by a chlorine atom, resulting in the formation of dichloromethane. Chloroform is formed from dichloromethane and carbon tetrachloride from chloroform in a similar manner. The reaction of a 1:1 ratio of methane and chlorine at 440°C (at this high temperature, homolytic fission of the chlorine–chlorine bond occurs without light) results in the product mixture shown in the following equation:

$$\underset{}{CH_4} + \underset{}{Cl_2} \xrightarrow{440°C} \underset{47\%}{CH_4} + \underset{20\%}{CH_3Cl} + \underset{22\%}{CH_2Cl_2} + \underset{10\%}{CHCl_3} + \underset{1\%}{CCl_4} + HCl$$

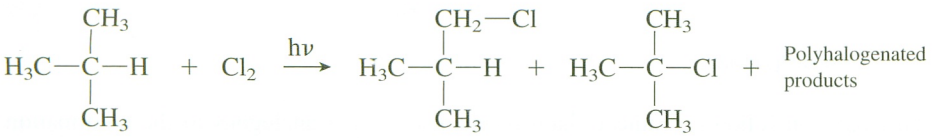
Because of the number of products that are produced, this reaction is not very useful in the laboratory. However, the chlorination of methane by this method is used industrially for the production of the various chloromethanes. After the reaction is completed, the hydrogen chloride is removed by treatment with water, and the mixture of products is separated by distillation. The methane is recycled, and the chlorinated products are sold.

PROBLEM 21.6

Show all of the steps in the mechanism for the formation of dichloromethane from chloromethane:

$$CH_3Cl + Cl_2 \longrightarrow CH_2Cl_2 + HCl$$

Another factor that limits the usefulness of the chlorination reaction in the laboratory is the lack of selectivity exhibited by the chlorine atom when more than one type of hydrogen is available to be abstracted. As an example, the reaction of isobutane with chlorine produces 1-chloro-2-methylpropane and 2-chloro-2-methylpropane in a 2:1 ratio, in addition to products containing more than one chlorine.

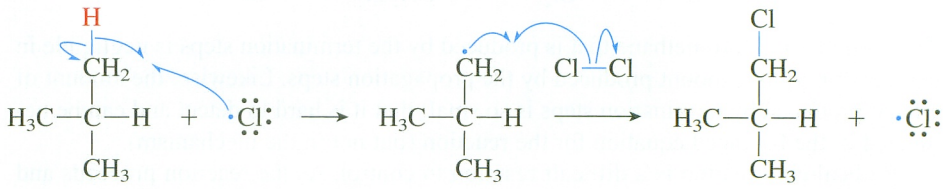


2 : 1

Isobutane — 1-Chloro-2-methylpropane — 2-Chloro-2-methylpropane

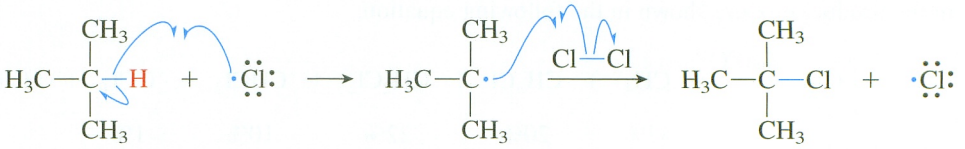
The formation of this mixture of products limits the usefulness of this reaction for laboratory synthesis.

Let's carefully analyze the reasons why these products are formed in this ratio. When a chlorine atom encounters an isobutane molecule, it may abstract a primary hydrogen, leading ultimately to the formation of 1-chloro-2-methylpropane:



A primary radical

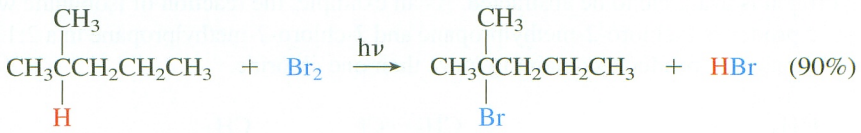
Or it may abstract the tertiary hydrogen, leading to the formation of 2-chloro-2-methylpropane:



A tertiary radical

There are nine primary hydrogens and only one tertiary hydrogen, so if the hydrogens were all equally reactive, the products should be formed in a 9:1 ratio. Because the observed ratio is 2:1, the tertiary hydrogen must be 4.5 times as reactive as a primary hydrogen under this set of experimental conditions. The tertiary hydrogen is more reactive than a primary hydrogen because the tertiary radical that is produced is more stable than a primary radical. Therefore, the transition state leading to the tertiary radical is somewhat lower in energy than the transition state leading to the primary radical. Although a chlorine atom has a slight preference to abstract a tertiary hydrogen over a secondary hydrogen and a slight preference to abstract a secondary hydrogen over a primary hydrogen, these preferences are small enough, and usually offset somewhat by statistical factors, that a mixture of products is usually formed.

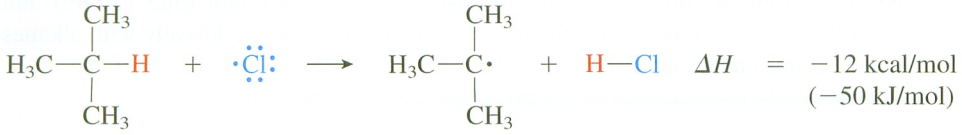
Bromine also reacts with alkanes in the presence of light to give products resulting from the substitution of a bromine for a hydrogen:

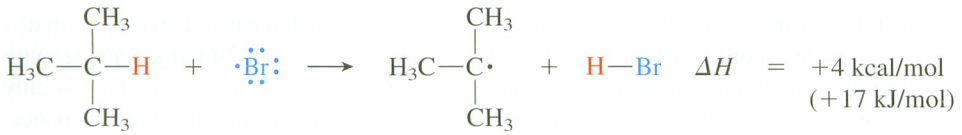


2-Methylpentane

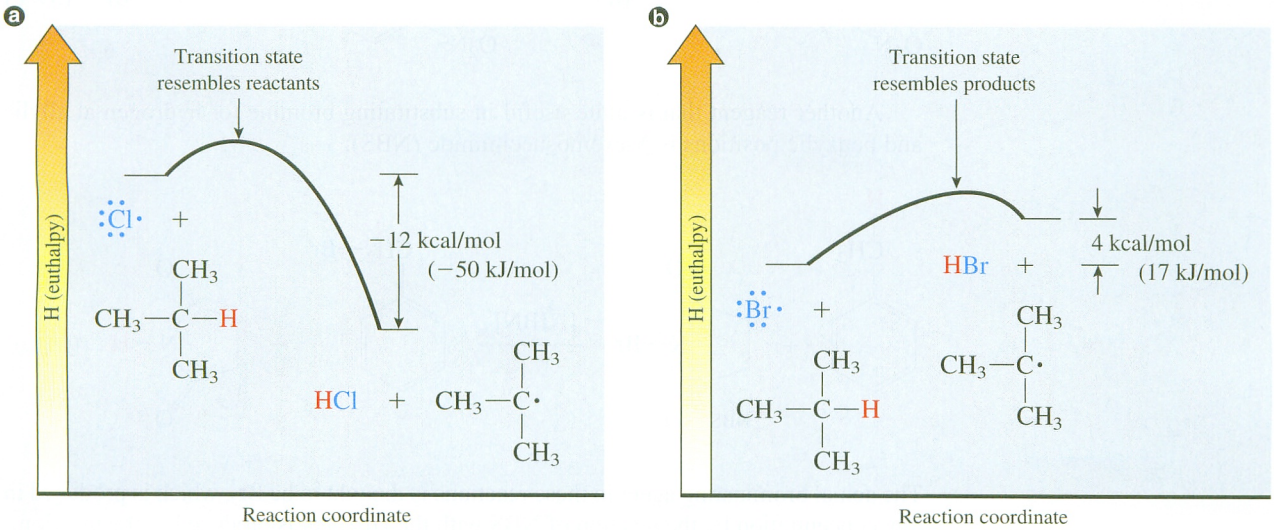
This reaction follows a radical chain mechanism that is analogous to the chlorination mechanism shown in Figure 21.1. However, as illustrated in this example, a bromine radical is much more selective than a chlorine radical. It greatly prefers to abstract a hydrogen from a tertiary carbon rather than from a primary or secondary carbon. This preference is large enough that a single product dominates in favorable cases such as the preceding example. Therefore, the bromination reaction is much more useful in synthesis.

Why is a bromine atom so much more selective than a chlorine atom in these hydrogen abstraction reactions? The answer can be found by examination of the energetics of each reaction. Because the bond strength of the hydrogen–chlorine bond (103 kcal/mol [413 kJ/mol]) is larger than the bond strength of the hydrogen–bromine bond (87 kcal/mol [364 kJ/mol]), the abstraction of a hydrogen by a chlorine atom is exothermic, whereas the abstraction of a hydrogen by a bromine atom is slightly endothermic. For example, the enthalpies for the abstraction of the tertiary hydrogen of isobutane by chlorine and by bromine are provided in the following equations:





According to the Hammond postulate, the transition state for abstraction by chlorine resembles the reactant because this is an exothermic reaction. In contrast, the transition state for abstraction by bromine resembles the product because it is an endothermic reaction (see Figure 21.2). In the case of abstraction by chlorine the carbon–hydrogen bond is only slightly broken in the transition state, and the stability



By the Hammond postulate, the transition state for abstraction of a hydrogen by a chlorine atom resembles the reactants and has only a small amount of radical character. Therefore, the transition state leading to a tertiary radical is only slightly more stable than the transition state leading to a primary radical.

In contrast, the transition state for abstraction of a hydrogen atom by a bromine atom resembles the product and has a large amount of radical character. Therefore, the transition state leading to a tertiary radical is considerably more stable than the transition state leading to a primary radical.

Figure 21.2

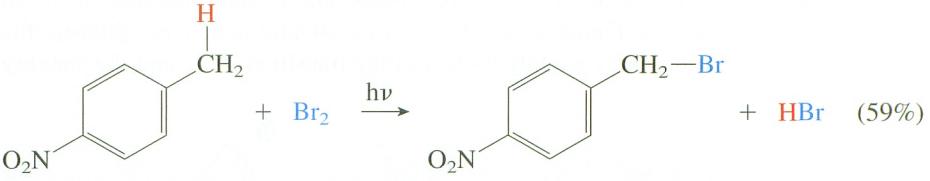
ENTHALPIES OF HYDROGEN ABSTRACTION BY (a) CHLORINE AND (b) BROMINE ATOMS.

of the product radical has only a small effect on the transition state energy. When a hydrogen is abstracted by bromine, the carbon–hydrogen bond is more broken in the transition state. The transition state has more radical character, so its energy is more affected by the stability of the radical product. In other words, a chlorine atom is more reactive than a bromine atom. Usually, the more reactive a reagent is, the less selective that reagent is.

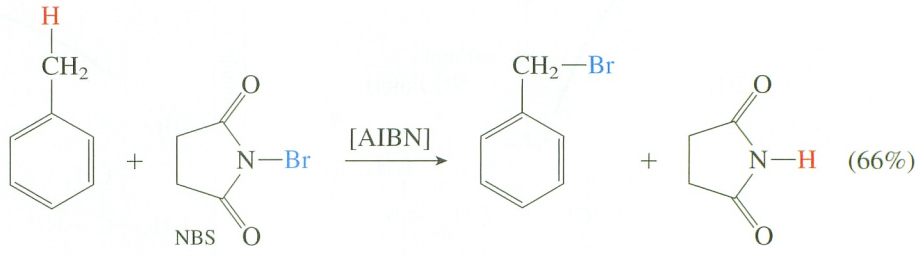
PROBLEM 21.7

The bond strengths for the HF and HI bonds are 135 kcal/mol (565 kJ/mol) and 71 kcal/mol (297 kJ/mol), respectively. Explain why F_2 reacts explosively with alkanes whereas I_2 does not react at all.

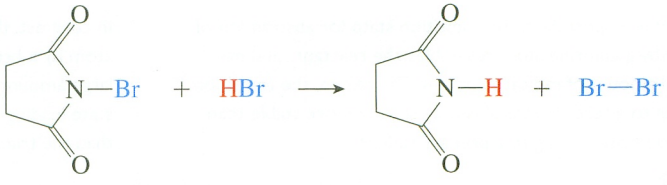
Because of the greater selectivity of the bromine atom, radical brominations can be useful in synthesis as long as the compound to be brominated has one hydrogen that is considerably more reactive than the others. The reaction of 2-methylpentane with bromine, shown previously, gives predominantly a single product because there is only one tertiary hydrogen. Because allylic and benzylic radicals are stabilized by resonance, bromination at these positions can also be successfully accomplished. An example is provided by the following equation:



Another reagent that is quite useful in substituting bromine for hydrogen at allylic and benzylic positions is *N*-bromosuccinimide (NBS):

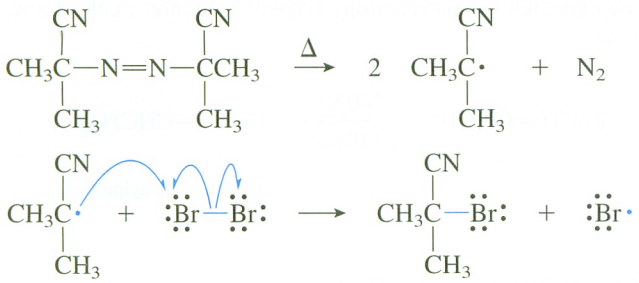


The actual brominating agent in these reactions is thought to be Br_2, which is produced in low concentration by the reaction of NBS with the HBr that is produced in the reaction:

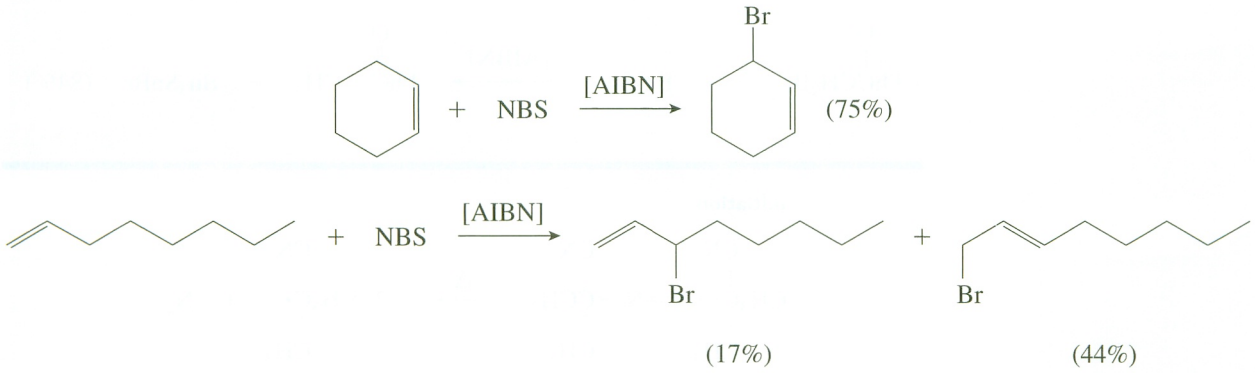


The mechanism then follows the same radical chain mechanism that is followed in other brominations with the exception that a radical initiator, such as AIBN or a peroxide, is

usually employed to initiate the reaction. The initiation steps are shown in the following equations:

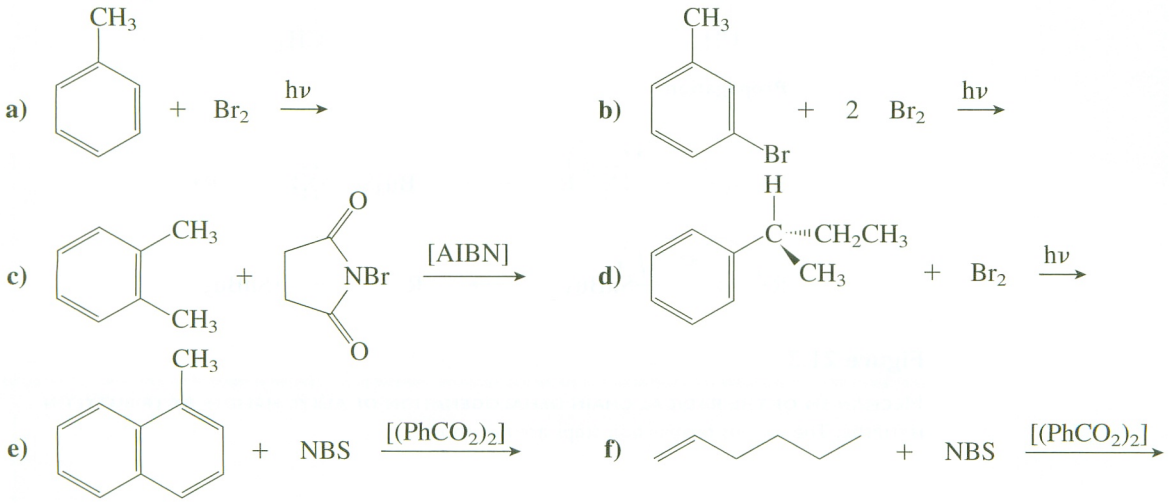


NBS has proved to be especially useful in brominations at allylic positions because competition from the addition of bromine to the double bond is not a problem. Apparently, the fact that only a low concentration of Br_2 is ever present in NBS brominations somehow inhibits the addition reaction. Examples are provided in the following equations. Note that the reaction is best if only a single type of allylic hydrogen is available to be abstracted. In addition, the resonance-stabilized allylic radical provides two sites that can abstract a bromine atom. If these two sites are different, a mixture of products is formed, as shown in the second example:



PROBLEM 21.8

Show the products of these reactions:



PROBLEM 21.9

The following reaction produces 3-bromo-1-phenylpropene in good yield. What other product might be expected in this reaction? Explain why not much, if any, of this other product is formed.

$$PhCH{=}CHCH_3 \xrightarrow[[AIBN]]{NBS} PhCH{=}CHCH_2Br$$

3-Bromo-1-phenylpropene

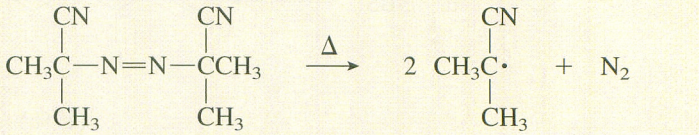
21.7 DEHALOGENATION

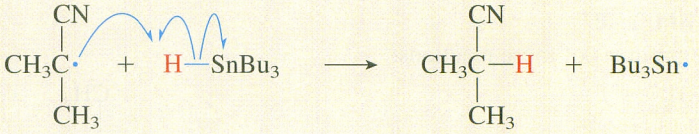
The reaction of an alkyl halide with tributyltin hydride, using a radical initiator, results in the replacement of the halogen by hydrogen. The reaction follows a radical chain mechanism as outlined in Figure 21.3. Examples are provided in the following equations:

$$PhCH_2CH_2Br + Bu_3SnH \xrightarrow{[AIBN]} PhCH_2\overset{H}{\overset{|}{C}}H_2 + Bu_3SnBr \quad (85\%)$$

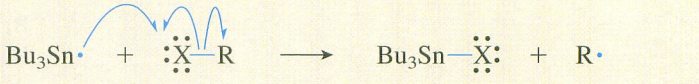
$$PhC(=O)CH_2Br + Bu_3SnH \xrightarrow{[AIBN]} PhC(=O)\overset{H}{\overset{|}{C}}H_2 + Bu_3SnBr \quad (84\%)$$

Initiation





Propagation



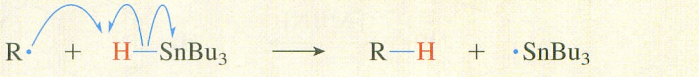
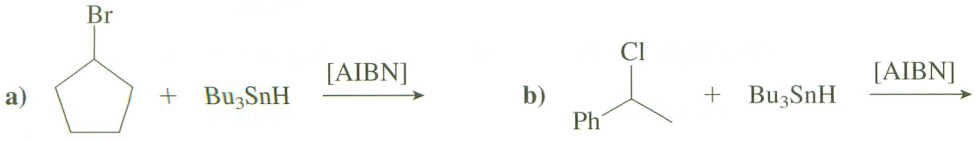


Figure 21.3

MECHANISM OF THE RADICAL CHAIN DEHALOGENATION OF ALKYL HALIDES BY TRIBUTYLTIN HYDRIDE. The various termination steps are not shown.

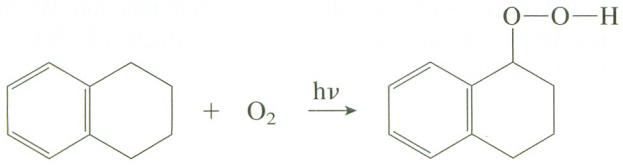
PROBLEM 21.10

Show the products of these reactions:



21.8 AUTOXIDATION

The slow oxidation of organic materials that are exposed to oxygen in the atmosphere is termed **autoxidation.** A simple example of this reaction is provided by the following equation:

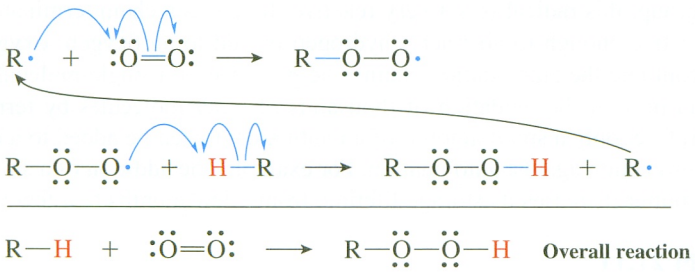


This process follows a radical chain mechanism and is catalyzed by light. (This is one reason why compounds are often sold and stored in brown glass bottles.) In the first step of the mechanism an initiating radical (In·) is generated by light or some other means. This radical abstracts a hydrogen from the substrate to produce a carbon radical (R·):

Initiation

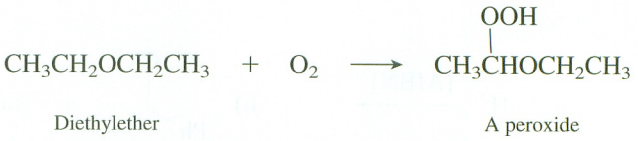
In the propagation steps, the carbon radical first adds to the oxygen–oxygen double bond to produce a peroxide radical. This radical abstracts a hydrogen from another molecule of the substrate, generating a hydroperoxide and another carbon radical that can repeat the propagation cycle:

Propagation



The autoxidation reaction is difficult to control, so it is not often used for synthetic purposes. However, it is a very important natural process. The slow deterioration of organic materials, such as rubber, paint, and oils, and that of many foods, such as butter

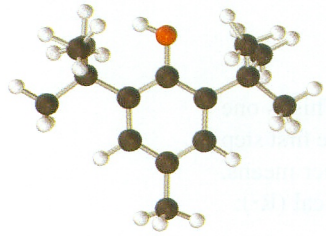
and fats, is due to autoxidation. As one example, peroxides are formed in solvents such as diethyl ether or THF that are stored for long periods of time in contact with air:

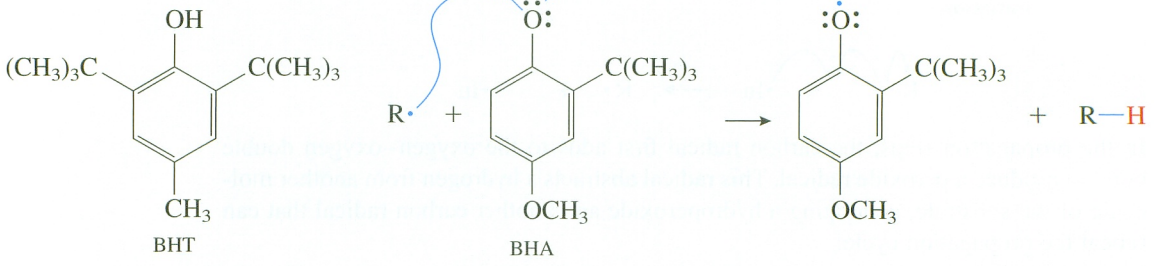


Diethylether — A peroxide

Because peroxides are explosive, the use of such contaminated solvents leads to a very dangerous situation. Numerous explosions have resulted in the laboratory when peroxides have been concentrated as the solvent is removed by distillation during the workup of a reaction. Therefore, it is important to be certain that ether and THF are free of peroxides before they are employed as solvents. Solutions of ether or THF should never be distilled to dryness.

Antioxidants, such as 2,6-di-*tert*-butyl-4-methylphenol (also known as butylated hydroxytoluene or BHT) and 2-*tert*-butyl-4-methoxyphenol (also known as butylated hydroxyanisole or BHA), are added to many organic materials to prevent autoxidation. They function by interfering with the autoxidation chain reaction. When a radical encounters an antioxidant molecule, such as BHA, it abstracts a hydrogen to produce a resonance-stabilized radical:





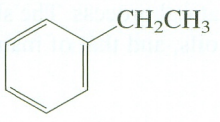
BHT — BHA

Because of this resonance stabilization and the steric hindrance provided by the bulky *tert*-butyl group, this radical is not very reactive. It acts as a chain terminator because it is not reactive enough to abstract a hydrogen or add to an oxygen–oxygen double bond and continue the autoxidation chain. The presence of a single molecule of BHA or BHT can prevent the oxidation of thousands of other molecules by terminating a chain. Therefore, only a small amount of an antioxidant need be added to a compound to provide protection against autoxidation. For example, the addition of a small amount of BHA to butter increases its storage lifetime from a few months to a few years.

PROBLEM 21.11

Predict the major product from autoxidation of these compounds:

a)

b) 

Focus On Biological Chemistry

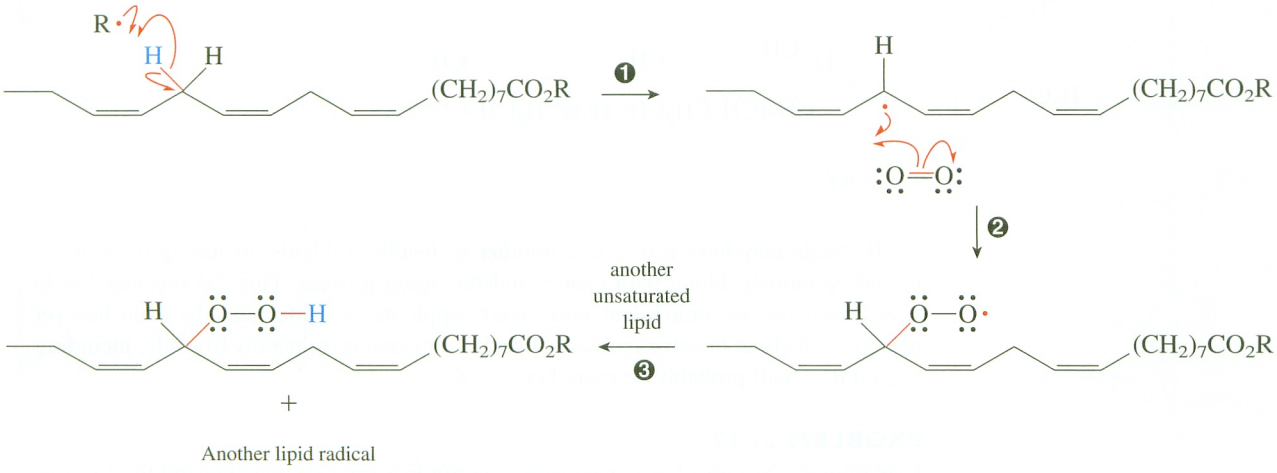
Vitamin E and Lipid Autoxidation

Glycerophospholipids are major components of biological membranes. They resemble the fats described in the Focus On box "Preparation of Soaps" on page 819 in that they are composed of esters of the triol glycerol with carboxylic acids (fatty acids) that have long hydrocarbon chains. In contrast to fats, however, glycerophospholipids have only two fatty acid groups attached to the glycerol. The third site is occupied by an ionic or highly polar group attached to the glycerol by an ester linkage. The hydrocarbon chains contribute hydrophobic character to the lipid, whereas the polar groups are hydrophilic. This combination of properties enables glycerophospholipids to form the bilayer membranes that are so important in biological systems.

The hydrocarbon chains of fatty acids often contain one or more cis double bonds. These unsaturated lipids are especially prone to autoxidation. An example is provided by the following equation, which shows an autoxidation reaction of the ester of α-linoleic acid. Note that this is a chain reaction, so one initiator can cause numerous lipid molecules to be oxidized.

❶ Some radical initiates the chain by abstracting a hydrogen atom. The allylic hydrogens of unsaturated lipids are especially susceptible to this process.

❷ The resulting radical adds to an oxygen molecule.



The new lipid radical continues the chain process.

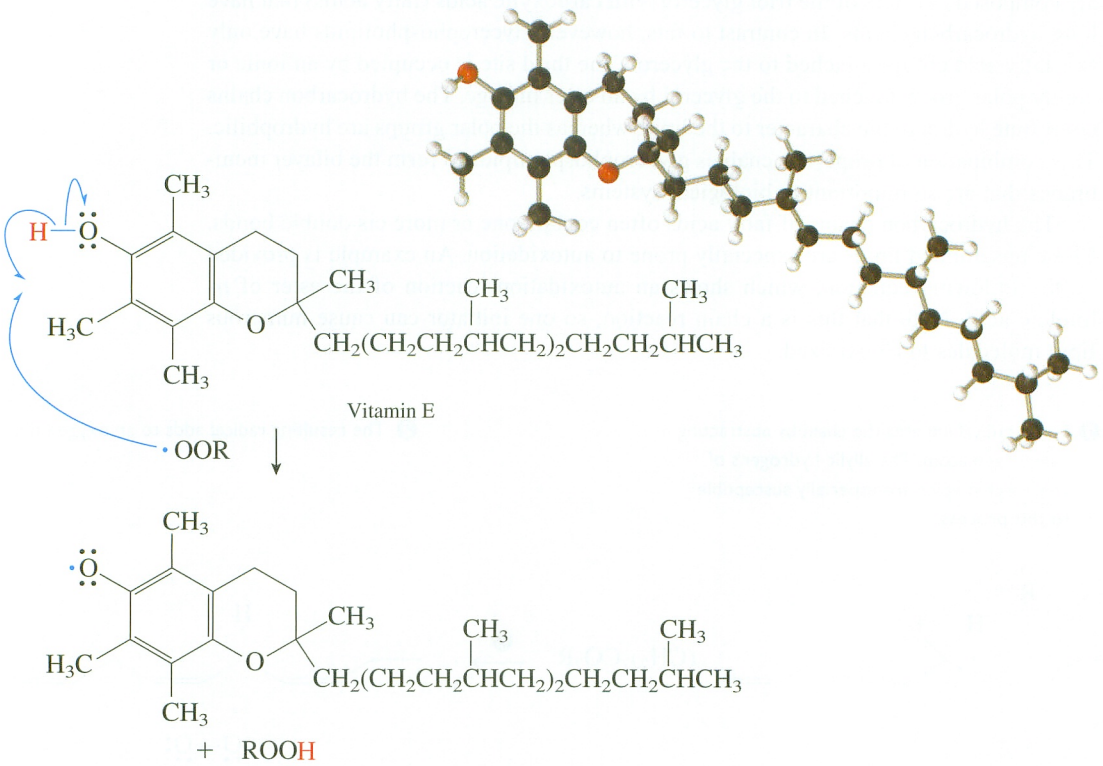
❸ This peroxy radical abstracts a hydrogen from a neighboring lipid molecule.

The peroxidized tails of these lipids are more hydrophilic and try to migrate to the surface of the membrane. This disrupts the structure of the membrane and makes it

Continued

"leaky." Similar peroxidation of unsaturated lipids in low-density lipoproteins is thought to contribute to arteriosclerosis and heart disease.

Nature has many defenses against unwanted oxidation reactions. Vitamin E, also known as α-tocopherol, helps to serve this role in human membranes. It is a hindered phenol, somewhat resembling BHT and BHA, and it is soluble in the membrane because of its nonpolar hydrocarbon tail. The radical that is produced when the hydrogen of its hydroxy group is abstracted is not very reactive, so vitamin E terminates autoxidation chains:



Radicals may have a role in a number of health problems, including those mentioned previously, along with cancer and the aging process. This has recently led to widespread use of antioxidant nutritional supplements. Unfortunately, little has yet been proved about the effectiveness of such supplements. A healthy lifestyle, including a good diet, will probably be more beneficial.

PROBLEM 21.12

Explain why the radical produced from vitamin E is not very reactive and thus acts as a chain terminator.

21.9 Radical Additions to Alkenes

In Chapter 11 the electrophilic addition of hydrogen bromide to alkenes, which proceeds by an ionic mechanism, was discussed. Recall that this reaction follows Markovnikov's rule and the bromine adds to the more highly substituted carbon, as illustrated in the following example:

$$CH_3CH_2CH_2CH_2CH{=}CH_2 + HBr \longrightarrow CH_3CH_2CH_2CH_2\overset{Br}{\underset{}{C}}H\overset{H}{\underset{}{C}}H_2 \quad (88\%)$$

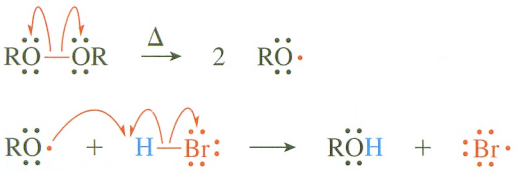
When a similar reaction occurs under conditions favoring the formation of radicals—that is, in the presence of light or a peroxide that can initiate the reaction—the addition still occurs, but with the opposite regiochemistry. The bromine adds to the less highly substituted carbon, and the addition is said to occur in an **anti-Markovnikov** manner. Examples are provided by the following equations:

$$CH_3CH_2CH{=}CH_2 + HBr \xrightarrow[\text{or } h\nu]{[ROOR]} CH_3CH_2\overset{H}{\underset{}{C}}H\overset{Br}{\underset{}{C}}H_2 \quad (95\%)$$

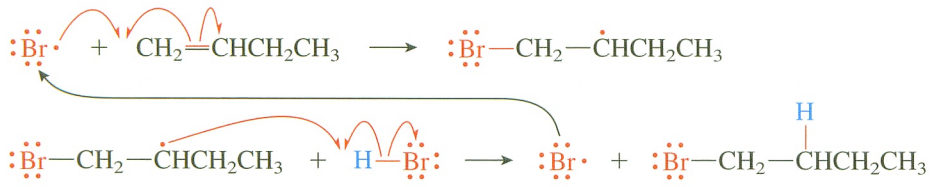
$$PhCH_2CH{=}CH_2 + H{-}Br \xrightarrow{[ROOR]} PhCH_2\overset{H}{\underset{}{C}}HCH_2{-}Br \quad (80\%)$$

The change in regiochemistry is a result of a change in the mechanism of the reaction, from an ionic mechanism in the Markovnikov reaction to a radical chain mechanism in the anti-Markovnikov reaction. The radical chain mechanism for the addition of hydrogen bromide to 1-butene is outlined in the following equations:

Initiation



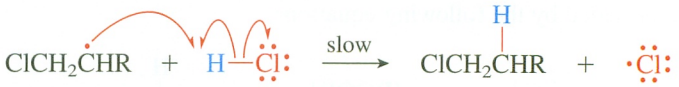
Propagation



In the propagation steps, a bromine atom first adds to the carbon–carbon double bond. The resulting carbon radical then abstracts a hydrogen from hydrogen bromide, generating a molecule of 1-bromobutane and a bromine atom that can continue the chain.

The regiochemistry of the product is controlled by the energetics of the step in which the bromine atom adds to the double bond. The bromine adds to the less substituted carbon so that a more stable radical, with the odd electron located on the more highly substituted carbon, is formed. Thus, radical stability controls the regiochemistry of this reaction in the same manner that carbocation stability controls the regiochemistry of the ionic reaction. In both reactions the adding species bonds to the less substituted carbon (the carbon that is bonded to more hydrogens), so the resulting carbocation, or radical, is more stable because the positive charge, or odd electron, is located on the more highly substituted carbon (the carbon bonded to more carbons). A proton electrophile adds in the ionic reaction, whereas a bromine radical adds in the radical reaction, so the two reactions have the opposite regiochemistry.

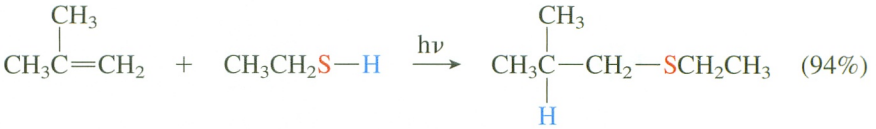
Hydrogen chloride and hydrogen iodide do not readily give this reaction because one of the propagation steps is slow. In the case of HCl the strong hydrogen–chlorine bond (bond dissociation energy = 103 kcal/mol [431 kJ/mol]) causes the abstraction step to be slow:



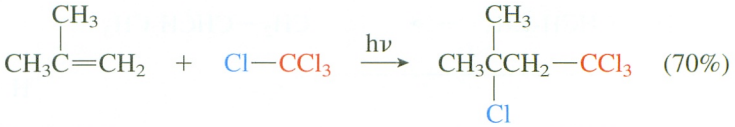
In the case of HI the weak carbon–iodine bond (bond dissociation energy = 52 kcal/mol [217 kJ/mol]) causes the addition step to be slow:

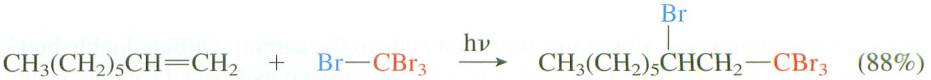
Only in the case of HBr do both propagation steps occur readily.

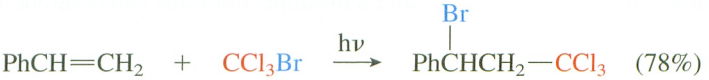
Other reagents can add to carbon–carbon double bonds in synthetically useful yields by similar radical chain mechanisms. The reaction of an alkene with a thiol under radical conditions results in the addition of the sulfur and a hydrogen to the carbons of the double bond:



Likewise, several tetrahalomethanes add a trihalomethyl group and a halogen to the carbons of the double bond of an alkene under radical conditions. Examples are provided in the following equations:

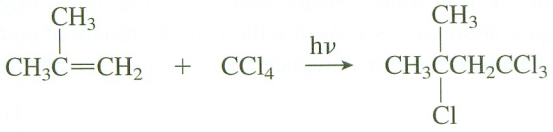






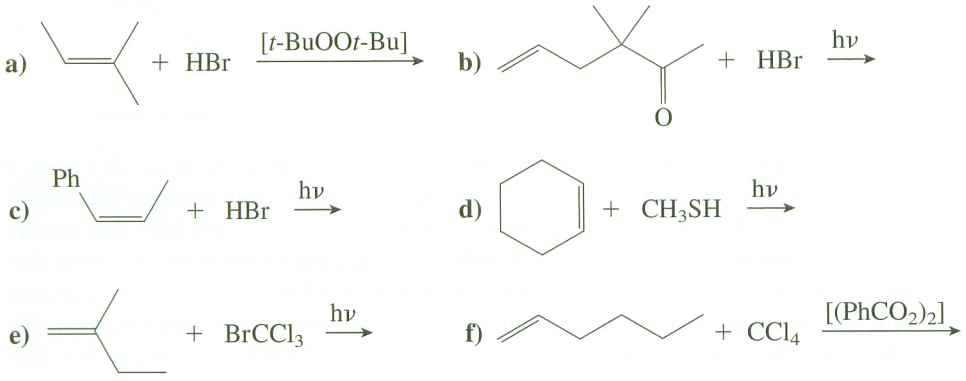
PROBLEM 21.13

Show all of the steps in the mechanism for this reaction:



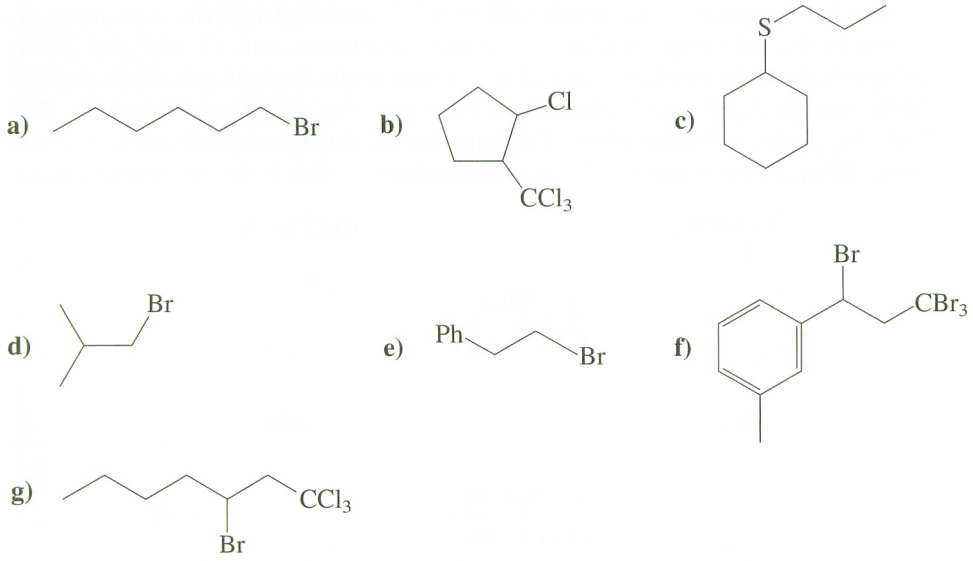
PROBLEM 21.14

Show the products of these reactions:



PROBLEM 21.15

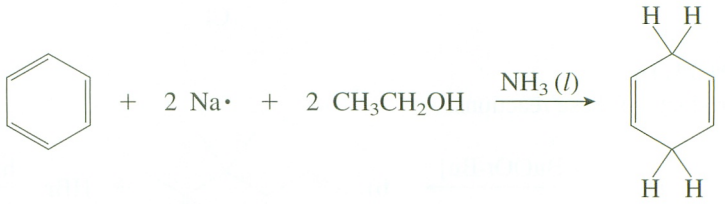
Show methods to prepare these compounds from alkenes:



21.10 REDUCTIONS AND RADICAL ANIONS

Many organic compounds can be reduced by reaction with a source of electrons and a source of protons. (Previous examples include the Clemmensen reduction and the reduction of nitro groups to amino groups described in Chapter 17.) Often this is accomplished

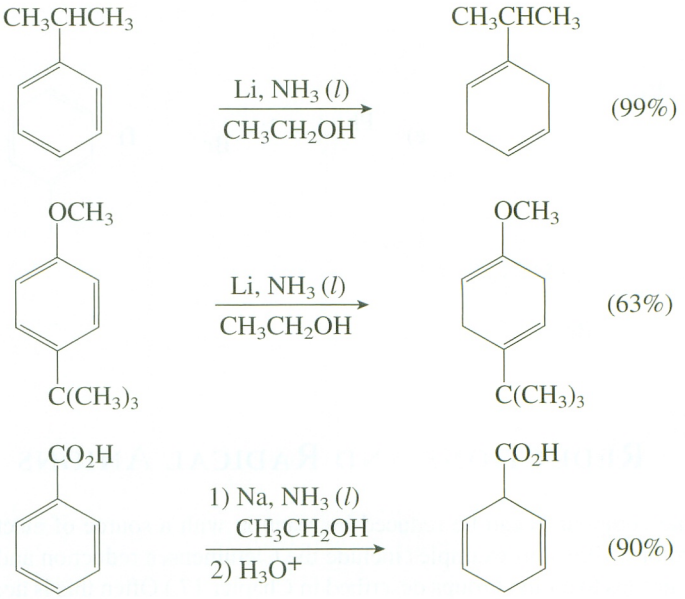
by employing electropositive metals as the electron source in the presence of a weak acid. A useful application of this process, known as the **Birch reduction,** employs sodium or lithium metal as the electron source for the reduction of aromatic rings. The reaction is usually done in liquid ammonia as solvent with a small amount of an alcohol present as the proton source. The benzene ring is reduced to a 1,4-cyclohexadiene derivative:



Benzene 1,4-Cyclohexadiene

The mechanism of the Birch reduction is shown in Figure 21.4. In the first step, a sodium atom gives an electron to a benzene molecule. This electron occupies the lowest-energy orbital in the benzene that has room for it, a pi antibonding (π^*) MO. This species is called a **radical anion** because it has both an odd number of electrons and a negative charge. The radical anion is strongly basic and is protonated by the alcohol that is present in the reaction to produce a radical. Another sodium atom donates a second electron to the radical, and the resulting anion is protonated by another alcohol molecule. In this final protonation step, the delocalized anion is protonated so as to form the nonconjugated product, 1,4-cyclohexadiene, rather than the conjugated product, 1,3-cyclohexadiene. The reasons for this preference are complex and beyond the scope of this book.

Several examples of the Birch reduction of substituted benzene derivatives are shown in the following equations. Note that substituents such as alkyl and alkoxy groups prefer to be attached to one of the carbons of the double bonds of the product, while a carboxyl group prefers to be attached to one of the singly bonded carbons. Benzene derivatives with other types of substituents are usually not employed as reactants in the Birch reduction because the substituents are not stable to the reaction conditions.



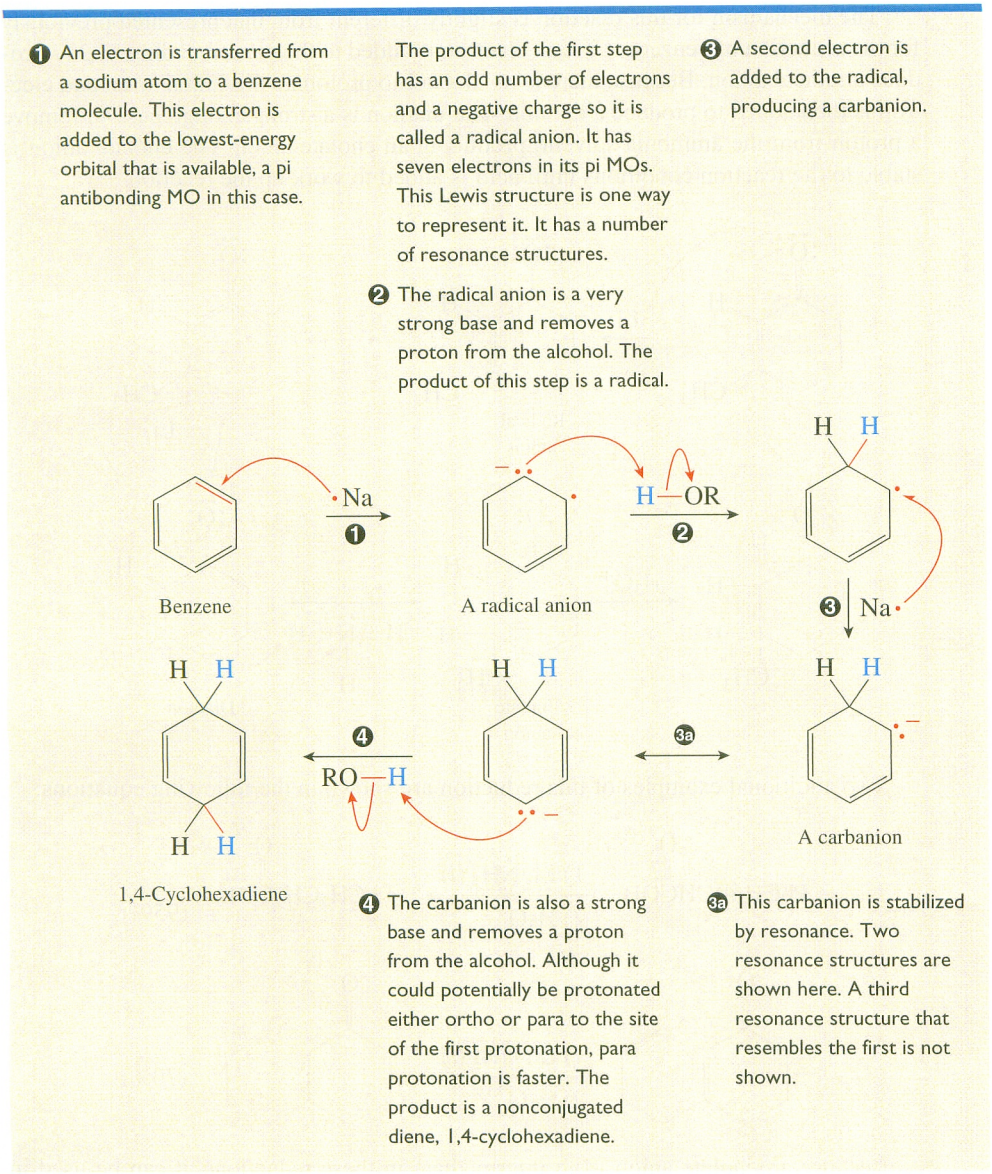
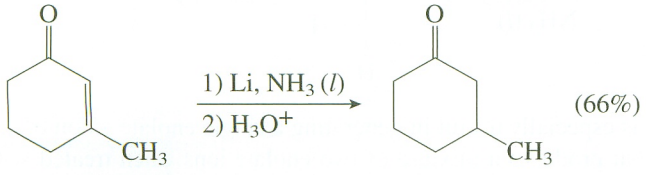

❶ An electron is transferred from a sodium atom to a benzene molecule. This electron is added to the lowest-energy orbital that is available, a pi antibonding MO in this case.
The product of the first step has an odd number of electrons and a negative charge so it is called a radical anion. It has seven electrons in its pi MOs. This Lewis structure is one way to represent it. It has a number of resonance structures.
❷ The radical anion is a very strong base and removes a proton from the alcohol. The product of this step is a radical.
❸ A second electron is added to the radical, producing a carbanion.
Na
H—OR
Benzene
A radical anion
H H
❸ Na
H H
H H
H H
H H
RO—H
❹
3a
1,4-Cyclohexadiene
A carbanion
❹ The carbanion is also a strong base and removes a proton from the alcohol. Although it could potentially be protonated either ortho or para to the site of the first protonation, para protonation is faster. The product is a nonconjugated diene, 1,4-cyclohexadiene.
3a This carbanion is stabilized by resonance. Two resonance structures are shown here. A third resonance structure that resembles the first is not shown.

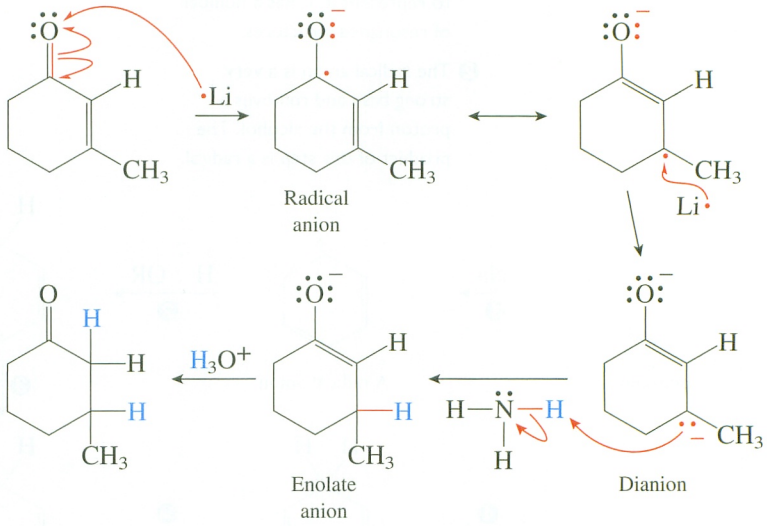
Figure 21.4

MECHANISM OF THE BIRCH REDUCTION OF BENZENE.

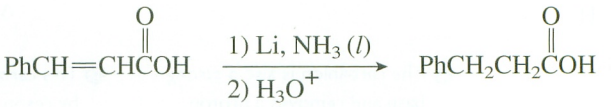
A normal alkene is not reduced under the conditions of the Birch reduction because its pi antibonding MO is too high in energy for an electron from a sodium atom to be readily added to it. However, as shown in the following example, a carbon–carbon double bond that is conjugated with a carbonyl group is readily reduced by lithium or sodium metal in liquid ammonia solvent, without any added alcohol.

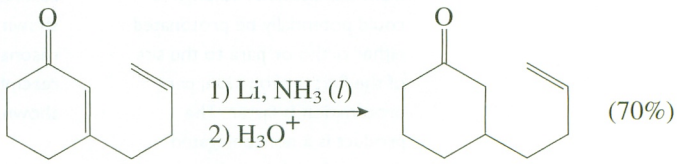


The mechanism for this reaction is slightly different from that presented previously for the reduction of benzene. First an electron is added to the pi antibonding MO to produce a radical anion. Because there is no alcohol to protonate this anion, a second electron is then added to produce a dianion. The dianion is a strong enough base to remove a proton from the ammonia solvent, producing an enolate anion. The enolate anion is stable to the reaction conditions until acid is added to work up the reaction.

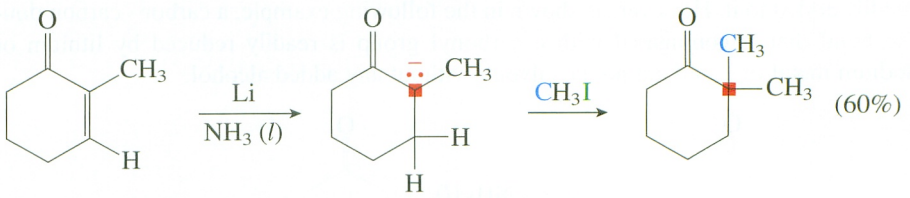


Two additional examples of this reduction are shown in the following equations:



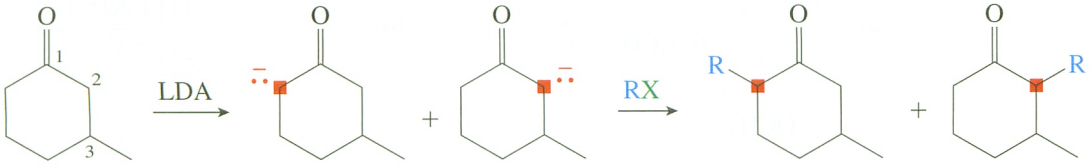


Because an enolate anion is an intermediate in these reductions, it can be used in synthesis in much the same manner as enolate anions that are generated by deprotonation (see Section 20.3). Thus, the addition of an alkyl halide to the reaction mixture after the reduction has been completed results in the alkylation of the enolate anion:



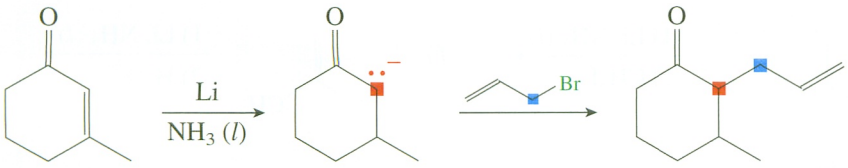
This reaction is especially useful in generating a single enolate anion of an unsymmetrical ketone that produces a mixture of two enolate ions when treated with base. This

allows the position of alkylation of unsymmetrical ketones to be controlled. As an example, suppose we want to alkylate 3-methylcyclohexanone at the 2 position. Direct alkylation is synthetically unattractive because treatment of the ketone with base results in the formation of two enolate ions, and two alkylation products are produced:



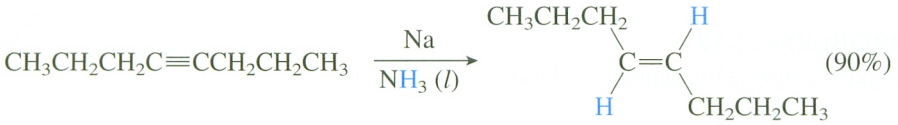
3-Methylcyclohexanone

However, the enolate anion can be generated specifically at the 2 position by reduction of 3-methyl-2-cyclohexenone. Addition of the alkyl halide results in the formation of a single alkylation product as illustrated in the following equation:



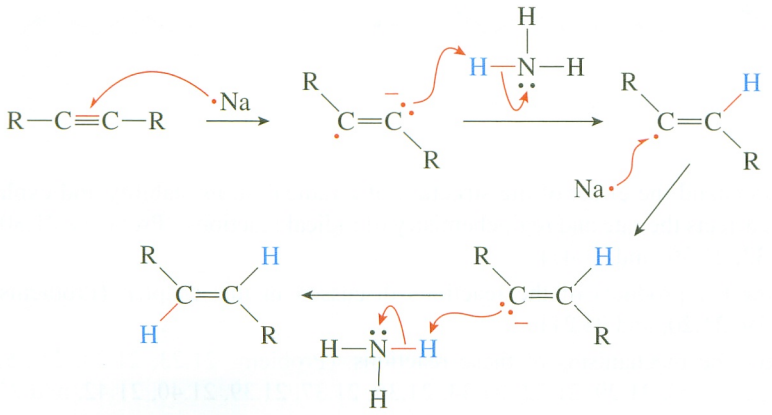
(47%)

Finally, the reduction of the carbon–carbon triple bond of an alkyne can also be accomplished by using sodium or lithium in liquid ammonia. This reaction is especially useful because it produces the (*E*)-isomer of the alkene product. (Recall that the (*Z*)-isomer can be prepared by catalytic hydrogenation of the alkyne; see Section 11.12.)



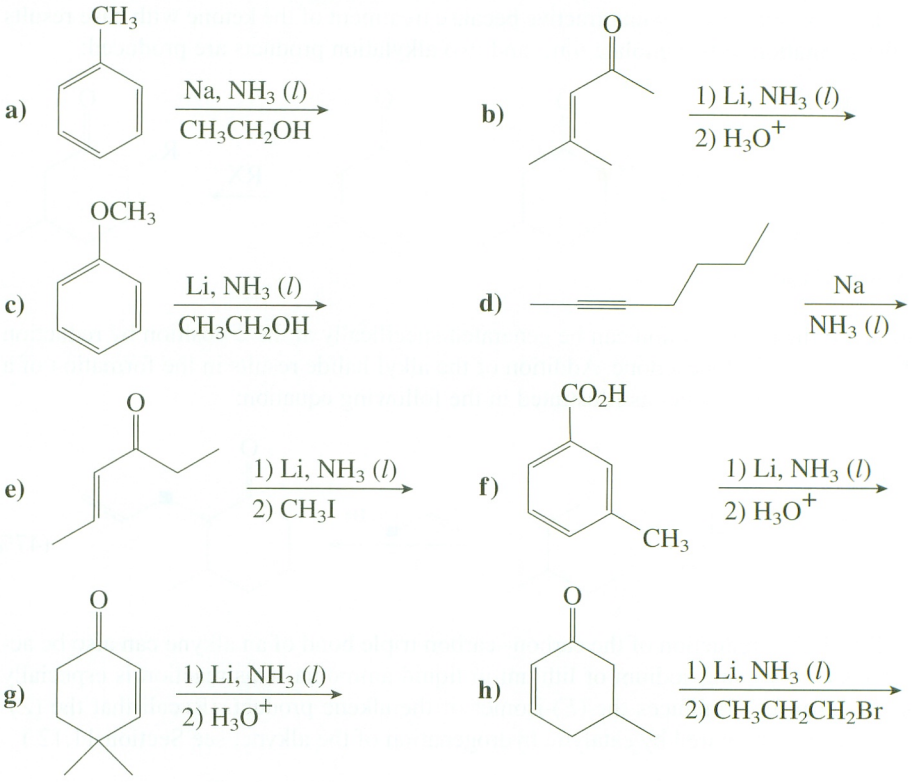
(90%)

Again, the mechanism proceeds by initial formation of a radical anion, which is then protonated by the ammonia solvent. The resulting radical accepts another electron from the sodium to produce an anion that has the bulky alkyl groups in a trans orientation. This anion removes a proton from another ammonia molecule to give the final product.



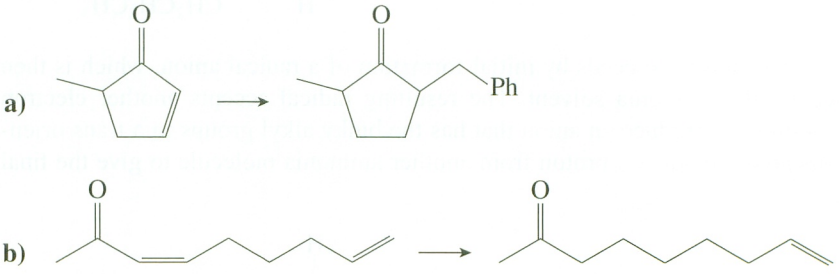
PROBLEM 21.16

Show the products of these reactions:



PROBLEM 21.17

Suggest reagents to accomplish these transformations:



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Review of Mastery Goals

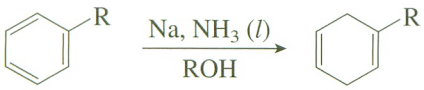
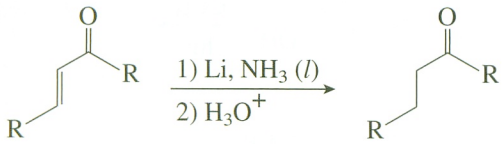
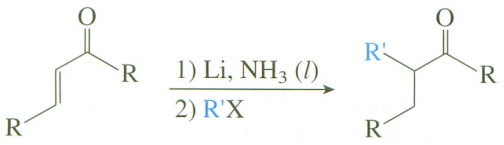
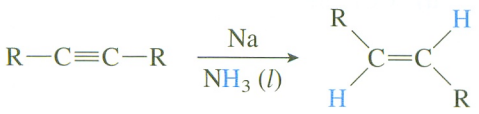
After completing this chapter, you should be able to:

- Understand the effect of the structure of a radical on its stability and explain how this affects the rate and regiochemistry of radical reactions. (Problems 21.30, 21.31, 21.33, 21.36, and 21.41)
- Show the products of the reactions discussed in this chapter. (Problems 21.18, 21.19, 21.20, and 21.21)
- Show the mechanisms of these reactions. (Problems 21.23, 21.24, 21.25, 21.26, 21.27, 21.28, 21.29, 21.32, 21.34, 21.35, 21.37, 21.39, 21.40, 21.42, and 21.43)
- Use these reactions in synthesis. (Problem 21.22)

Visual Summary of Key Reactions

The reactions presented in this chapter involve radicals as intermediates. They are summarized in Table 21.2. The use of light or an initiator, such as a peroxide or an azo compound (AIBN), is a key to recognizing radical reactions. The effect of structure on the stability of radical intermediates parallels the effect on carbocation stability.

Table 21.2 Summary of Radical Reactions

Reaction	Comments
$R{-}H + Cl_2 \xrightarrow{h\nu} R{-}Cl$	**Section 21.6** Chain mechanism, not very selective, multiple chlorinations occur
$R{-}H + Br_2 \xrightarrow{h\nu} R{-}Br$	**Section 21.6** Chain mechanism, more selective, can use NBS + initiator
$R{-}X + Bu_3Sn{-}H \xrightarrow{[AIBN]} R{-}H$	**Section 21.7** Chain mechanism
$R{-}H + O_2 \xrightarrow{h\nu} R{-}OOH$	**Section 21.8** Autoxidation, chain mechanism, not very selective
$R{-}CH{=}CH_2 + HBr \xrightarrow{[ROOR]} R{-}\underset{\displaystyle H}{\underset{\displaystyle \vert}{CH}}{-}\underset{\displaystyle Br}{\underset{\displaystyle \vert}{CH_2}}$	**Section 21.9** Anti-Markovnikov addition, chain mechanism, HCl and HI do not add
$R{-}CH{=}CH_2 + R'SH \xrightarrow{h\nu} R{-}\underset{\displaystyle H}{\underset{\displaystyle \vert}{CH}}{-}\underset{\displaystyle SR'}{\underset{\displaystyle \vert}{CH_2}}$	**Section 21.9** Anti-Markovnikov addition, chain mechanism
$R{-}CH{=}CH_2 + CX_4 \xrightarrow{h\nu} R{-}\underset{\displaystyle X}{\underset{\displaystyle \vert}{CH}}{-}\underset{\displaystyle CX_3}{\underset{\displaystyle \vert}{CH_2}}$	**Section 21.9** Chain mechanism
	**Section 21.10** Birch reduction, Li can also be used, radical anion mechanism
	**Section 21.10** Radical anion mechanism
	**Section 21.10** Alkylation of enolate anion
	**Section 21.10** *Trans*-alkene is formed

Many of the reactions presented in this chapter follow radical chain mechanisms. Such mechanisms consist of three types of steps: initiation, propagation, and termination. One initiation step results in a very large number of propagation steps, followed by a single termination step. The presence of a small amount of a chain inhibitor, such as an antioxidant, can prevent a chain reaction from occurring.

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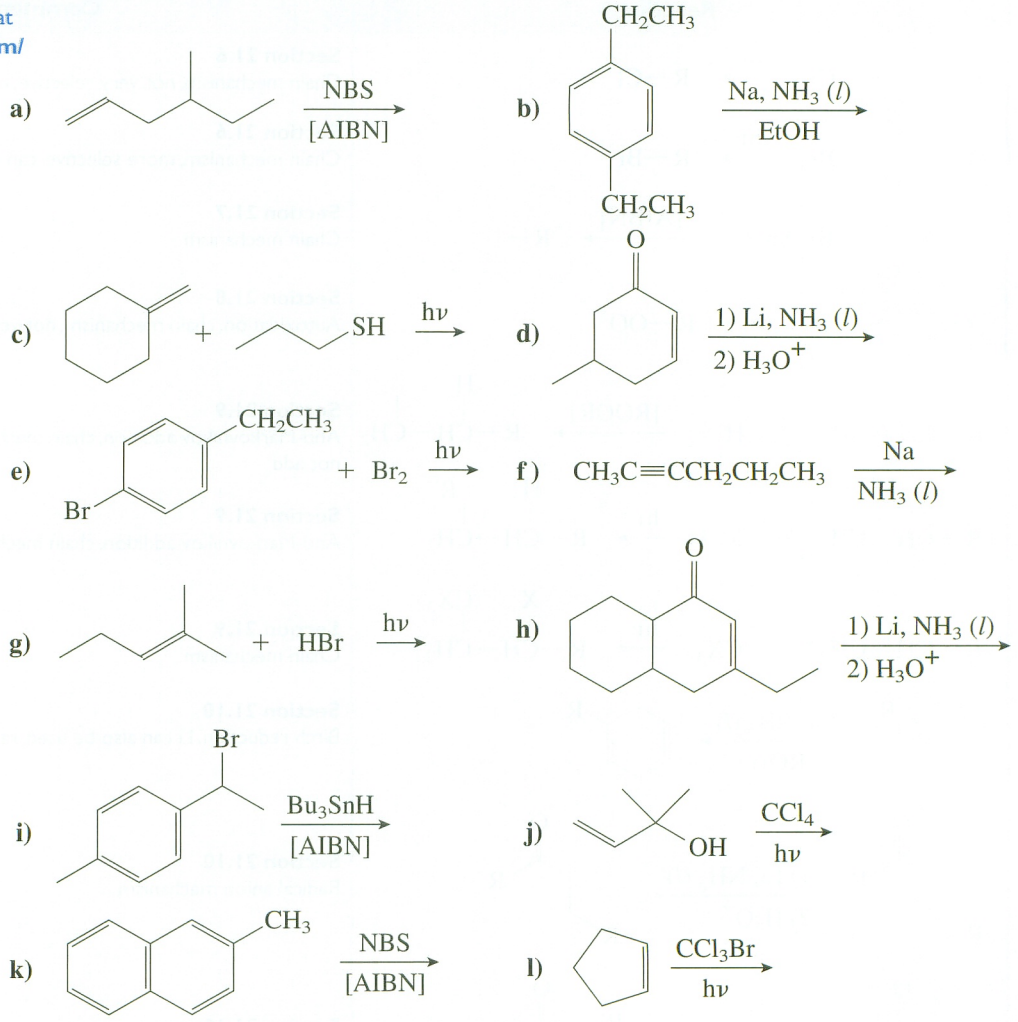
Additional Problems

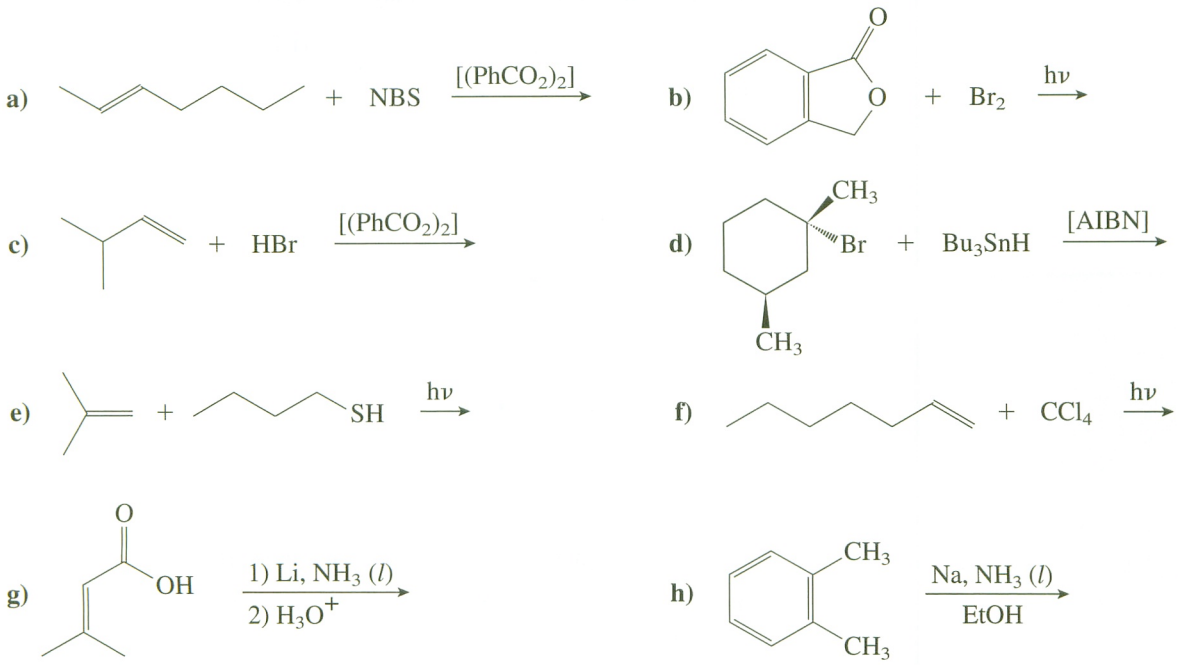
21.18 Show the products of these reactions.



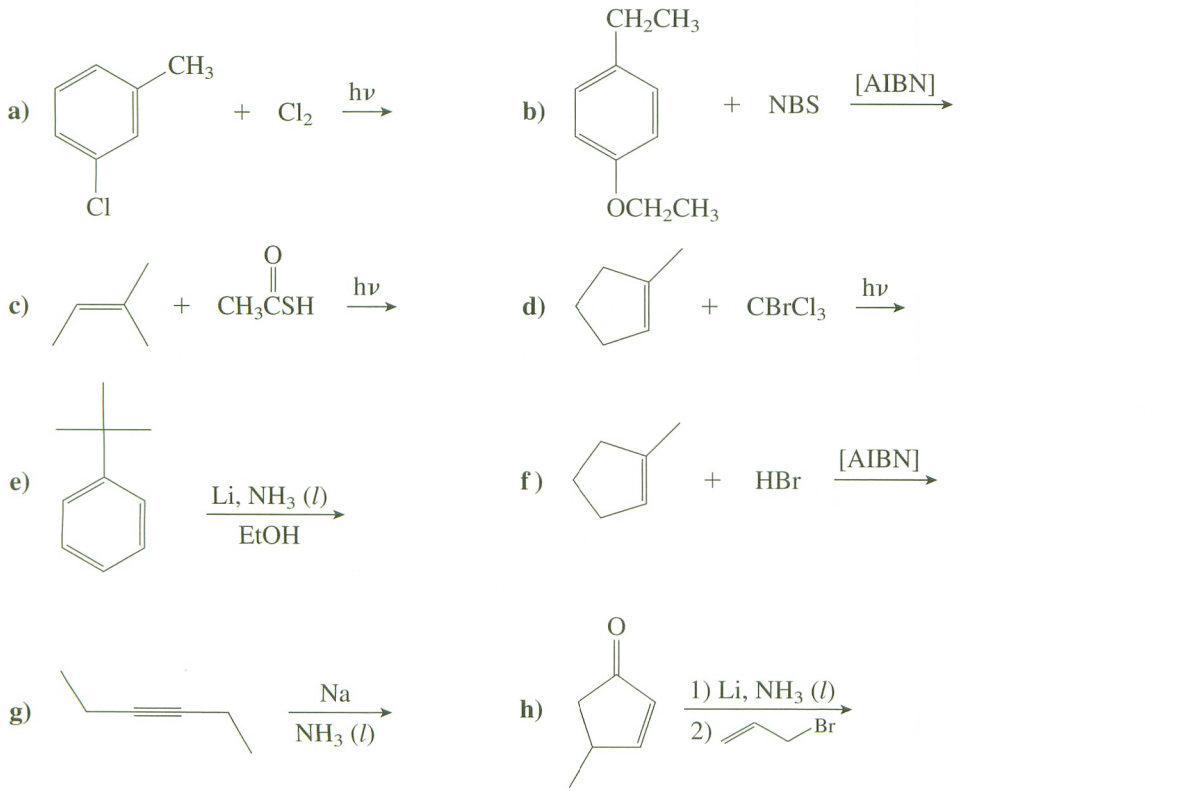
21.19 Show the products of the reactions of 1-hexene with each of these reagents:

a) NBS, [AIBN]
b) HBr, [*t*-BuOO*t*-Bu]
c) CH_3CH_2SH, hν
d) CCl_4, hν
e) $CBrCl_3$, hν

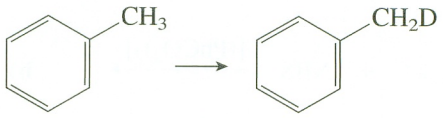
21.20 Show the products of these reactions:

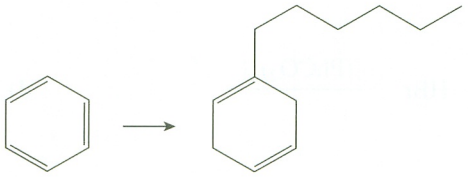


21.21 Show the products of these reactions:



21.22 Show syntheses of these compounds from the indicated starting materials. Reactions from previous chapters may be needed in some cases.

a) 

b) 

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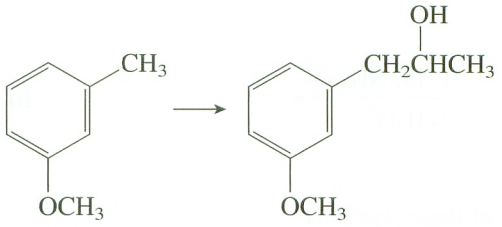
d) 

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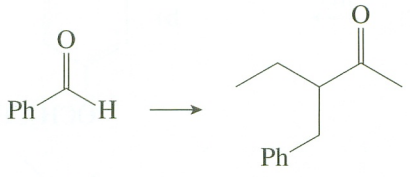
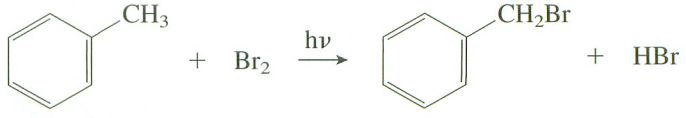
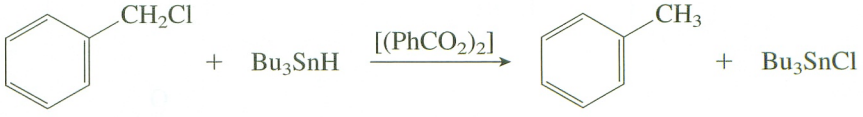
f) 

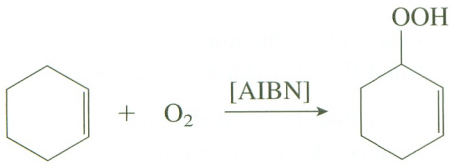
21.23 Show all of the steps in the mechanism for this reaction:



21.24 Show all of the steps in the mechanism for this reaction:

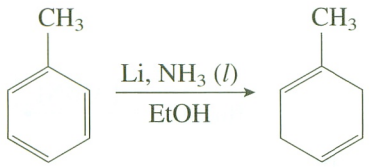


21.25 Show all of the steps in the mechanism for this reaction:

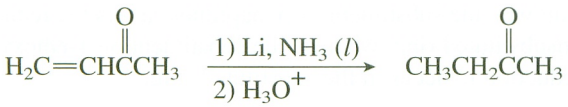


21.26 Show all of the steps in the mechanism for this reaction:

21.27 Show all of the steps in the mechanism for this reaction:



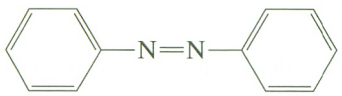
21.28 Show all of the steps in the mechanism for this reaction:



21.29 The following reaction gives three monobromo products. Show the structures of these products and explain their formation.

21.30 Radicals do not usually rearrange because the increase in stability is usually too small to provide sufficient driving force. Use the data in Table 21.1 to estimate the amount of heat that would be given off if this rearrangement were to occur:

21.31 Explain why azobenzene is not very useful as an initiator for radical reactions.

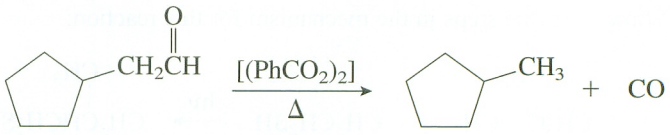


Azobenzene

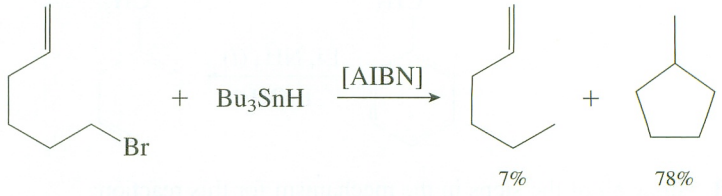
21.32 What reaction do you suppose occurs when O_2 is bubbled through a solution of the triphenylmethyl radical?

21.33 The product of a Birch reduction is 1,4-cyclohexadiene. Offer a reason why this product is not further reduced under the reaction conditions.

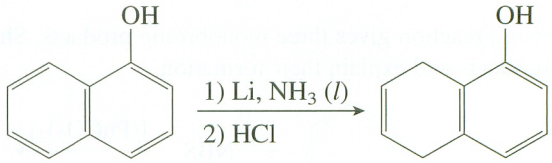
21.34 The following reaction has been shown to occur by a radical chain process. Suggest a mechanism for this process.

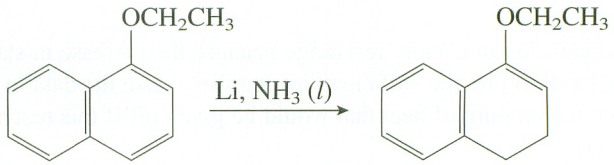


21.35 Suggest a mechanism that explains the formation of both of the products of this reaction:

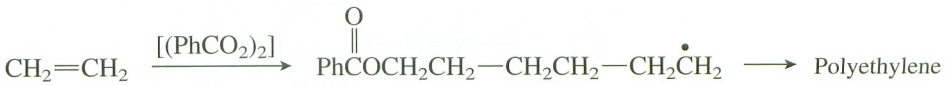


21.36 Explain why the substituent on 1-naphthol causes the reduction to occur in the unsubstituted ring, whereas the substituent on 1-ethoxynaphthalene causes the reduction to occur in the substituted ring.

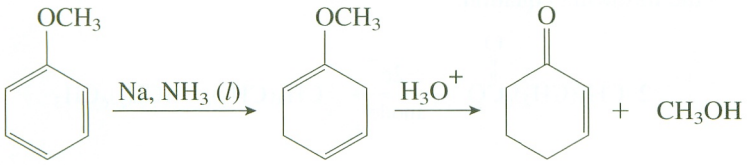




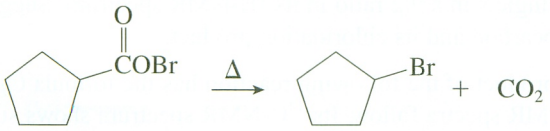
21.37 The reaction of alkenes with a small amount of a radical initiator is a common method used to prepare polymers (see Chapter 24). An intermediate stage in the formation of polyethylene is shown in this equation. Show a mechanism for the formation of this intermediate.



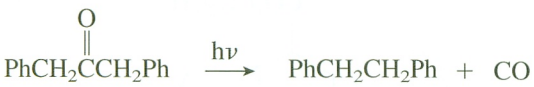
21.38 The Birch reduction of anisole, followed by reaction with acid, provides a useful method for the preparation of cyclohexenones. Show a mechanism for the hydrolysis step of this process.



21.39 The following reaction, known as the Hunsdiecker reaction, proceeds by a radical chain mechanism. Show the steps in this mechanism. (*Hint:* The weakest bond in the compound, the oxygen–bromine bond, is broken in the initiation step.)

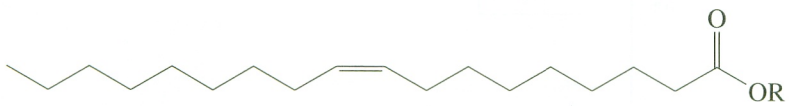


21.40 Suggest a mechanism for this photochemical reaction:



21.41 Esters of the fatty acid oleic acid are components of membranes that are subject to autoxidation. Explain which hydrogens of an oleate ester you expect to be abstracted most readily by a radical. Show the structures of the major autoxidation products that would be formed from an oleate ester.

BioLink



An oleate ester

21.42 Ozone, produced in the stratosphere by the action of ultraviolet light on O_2, helps shield the surface of the earth from harmful ultraviolet radiation. Ozone is slowly decomposed by reaction with oxygen atoms according to the following equation:

BioLink

Chlorofluorocarbons, such as CF_3Cl, catalyze this reaction and are responsible for the formation of the "ozone hole." The decomposition is a chain reaction involving chlorine atoms as the chain-carrying species. Suggest a mechanism for this reaction.

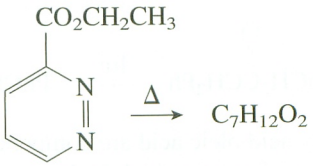
21.43 Carboxylate anions are oxidized at the anode of an electrochemical cell to produce radicals and ultimately hydrocarbons in a reaction known as the Kolbe electrolysis. Suggest a mechanism for the Kolbe electrolysis shown in the following equation:

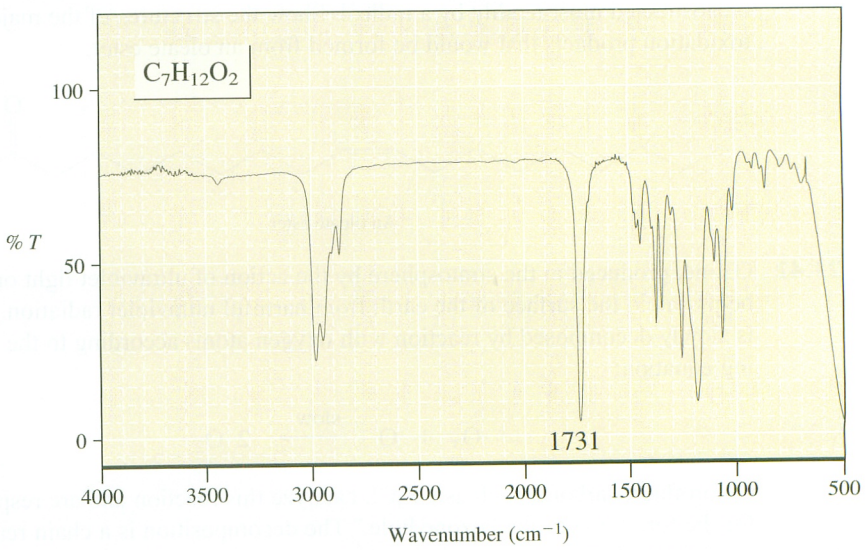
$$2\ CH_3(CH_2)_6\overset{\overset{O}{\|}}{C}O^- \xrightarrow[\text{anode}]{-2e^-} CH_3(CH_2)_6{-}(CH_2)_6CH_3 + 2\ CO_2$$

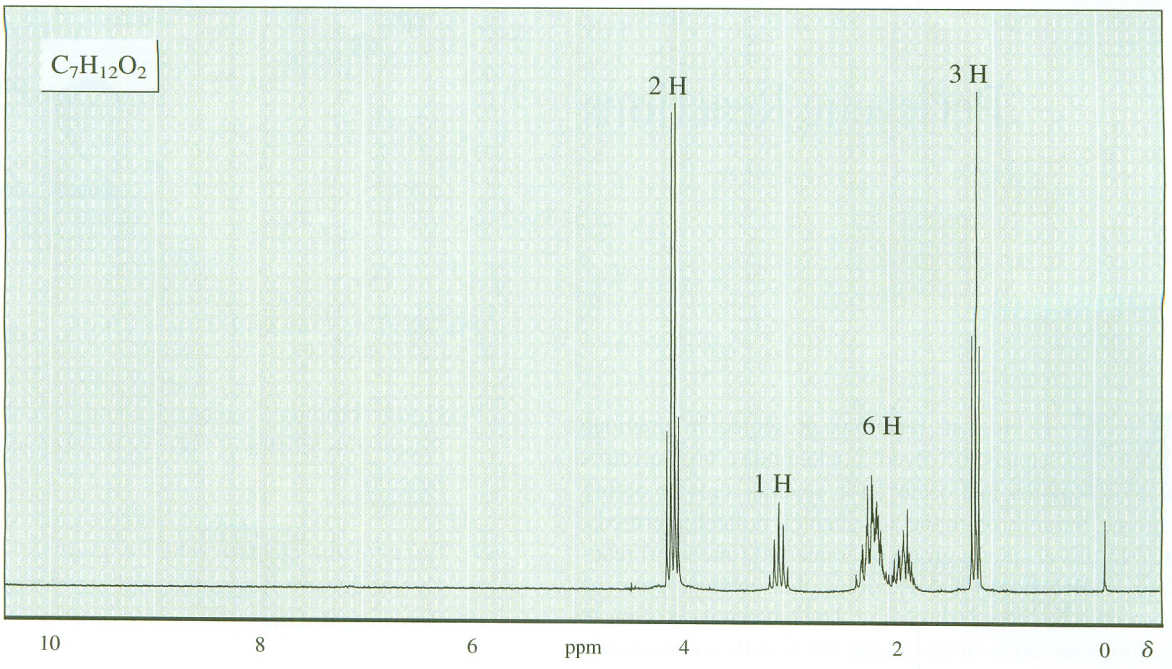
Problems Involving Spectroscopy

21.44 A hydrocarbon with the formula C_5H_{12} gives a single monochloro substitution product when reacted with Cl_2 in the presence of light. This product shows two singlets in a 9:2 ratio in its ^{1}H-NMR spectrum. Suggest structures for the hydrocarbon and its chlorination product.

21.45 The product of the following reaction has the formula $C_7H_{12}O_2$. Its IR and ^{1}H-NMR spectra follow. Its ^{13}C-NMR spectrum shows six absorptions. Show the structure of the product and suggest a mechanism for its formation.







Problems Using Online Three-Dimensional Molecular Models

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21.46 Radical A, shown here, is related to the triphenylmethyl radical by having oxygen atoms bridging the ortho positions of the phenyl groups. This radical dimerizes much faster than the triphenylmethyl radical. Explain this observation.

21.47 Galvinoxyl is a relatively unreactive radical. It is stable to oxygen, stable for extended storage as a solid, and decomposes only slowly in solution. Explain which atoms have radical electron density in galvinoxyl and explain why it is so unreactive.

21.48 Free radical chlorination (Cl_2 and light) of (*R*)-1-chloro-2-methylbutane gives the two products shown, in addition to other products. These two products are always formed in exactly equal amounts. Explain this observation.

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